Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Macrolides
Single Entity Agents
AHFS 081212
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I. Overview

Erythromycin, the first macrolide antibiotic, was isolated from products produced by *Streptomyces erythreus* in 1952. Erythromycin, which is still the most widely used macrolide antibiotic, and troleandomycin were the only members of this group until the early 1990s. In 1991, two semisynthetic derivatives of erythromycin, azithromycin (Zithromax®) and clarithromycin (Biaxin®), were marketed. Dirithromycin (Dynabac®) reached the market in 1995.

Macrolide antibiotics inhibit bacterial protein synthesis by binding to the 50 S ribosomal subunit. Macrolides are mainly bacteriostatic, but can be bacteriocidal depending on bacterial sensitivity and antibiotic concentration. Generally, macrolides are active against gram-positive cocci (mainly staphylococci and streptococci) and bacilli, and to lesser-extent gram-negative cocci. With the exception of Bordetella pertussis, Campylobacter, Chlamydia, Helicobacter, and Legionella species, gram-negative bacilli are generally resistant to the macrolides. Macrolides are also active against mycobacteria, mycoplasma, ureaplasma, spirochetes, and other organisms.

Erythromycin is available in a variety of salts and dosage forms. Erythromycin lactobionate is parenterally administered. Ethylsuccinate, estolate, stearate, and erythromycin base are administered orally. Various salts are available in an attempt to increase oral bioavailability. Erythromycin is metabolized by hepatic cytochrome P450; therefore it may interact with drugs metabolized by the cytochrome P450 system.[1]

Azithromycin and clarithromycin oral bioavailabilities are superior to erythromycin. Although azithromycin is not metabolized, clarithromycin is metabolized to a compound with bioactivity similar to that of erythromycin. Azithromycin and clarithromycin exhibit significant tissue penetration and are generally active against organisms that are usually susceptible to erythromycin; however, they possess greater intrinsic activity against *Haemophilus influenzae*. Azithromycin and clarithromycin are also concentrated within macrophages, making them useful against organisms that are taken up by macrophages, such as *Mycobacterium avium* intracellulare. Azithromycin and clarithromycin cause fewer gastrointestinal adverse reactions than erythromycin. Similar to erythromycin, clarithromycin is metabolized by hepatic cytochrome P450 microsomal enzymes and has the potential to interact with other drugs. Azithromycin has had few interactions reported clinically.[1, 2] This review encompasses all dosage forms and strengths.

Table 1. Single Entity Macrolide Antibiotics in this Review[3]

GENERIC NAME	FORMULATION	EXAMPLE BRAND NAME (S)
Azithromycin	Oral and injection	Zithromax®, Z-Pak®
Clarithromycin	Oral	Biaxin®, Biaxin XL®
Dirithromycin	Oral	Dynabac®
Erythromycin	Oral	*E-Mycin®, EryPed®, *ERYC, PCE® *E.E.S.® 200 and 400
Erythromycin Lactobionate*	Injectable	Erythrocin®

*Generic Available.

II. Evidence Based Medicine and Current Treatment Guidelines

The following is a brief representation of treatment guidelines containing the macrolide antibiotics.

Table 2. Treatment Guidelines Using the Macrolide Antibiotics

Clinical Guideline	Recommendation
Hospital Pharmacist Consensus Reports: The Antibiotic Selection for Community –Acquired Pneumonia Consensus Panel (The ASCAP Panel), 2002[3]	First-line treatment of patients with community-acquired pneumonia (CAP) is oral azithromycin, with quinolone antibiotics as alternative first-line therapy. Severe CAP complicated by structural disease of the lung, and increased pseudomonas and polymicrobial infection, should be treated with cefepime plus levofloxacin plus/minus an aminoglycoside **or** ciprofloxacin plus an aminoglycoside plus azithromycin. Alternatively, CAP can be treated with ciprofloxacin plus cefepime plus azithromycin **or** a carbapenem plus azithromycin plus an aminoglycoside. Patients with severe pneumonia requiring ICU hospitalization may also be treated alternatively with a carbepenem plus an aminoglycoside plus azithromycin.
Infectious Diseases Society of America: Guidelines for community-acquired pneumonia in immunocompetent adults, 2003[4]	Initial empiric therapy involving drugs in this class for suspected bacterial community-acquired pneumonia include: • Inpatient, medical ward with no recent antibiotic therapy; give a quinolone alone or an advanced macrolide (clarithromycin or azithromycin) plus a ß-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem). • ICU, pseudomonas is not an issue; give a ß-lactam plus either an advanced macrolide or a quinolone. • ICU, pseudomonas is an issue; give either (1) an antipseudomonal agent (piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime) plus ciprofloxacin or (2) an antipseudomonal agent plus an aminoglycoside plus a quinolone or a macrolide. • ICU, pseudomonas is an issue but patient has ß-lactam allergy; give either (1) aztreonam plus levofloxacin or (2) aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside.

Table 3. Comparison of Bacterial Coverage of the Single Entity Macrolide Antibiotics[1]

Drug	Spectrum
Azithromycin	Azithromycin is generally active against organisms that are usually susceptible to erythromycin. These include gram-positive organisms, such as *Staphylococcus aureus, Streptococcus agalactiae, S. pyogenes,* and *S. pneumoniae*, and gram-negative *Haemophilus influenzae* and *Moraxella catarrhalis*. *Chlamydia trachomatis* is also susceptible to azithromycin. Other organisms that have shown in vitro susceptibility include streptococci (Groups C, F, G), *Streptococcus viridans* group, *Bordetella pertussis, Campylobacter jejuni, Haemophilus ducreyi, Legionella pneumophilia, Bacteroides bivius, Clostridium perfringens, Peptostreptococcus species, Mycoplasma pneumoniae, Treponema pallidum*, and *Ureaplasma urealyticum.* The excellent tissue penetration and very low MIC of azithromycin against *Borrelia burgdorferi* (the causative agent of Lyme disease) suggest it may be highly useful in treating this serious disease.
Clarithromycin	Clarithromycin is generally active against organisms that are usually susceptible to erythromycin. These include most staphylococcal and streptococcal strains. In addition, clarithromycin is active against Moraxella catarrhalis, Mycoplasma pneumoniae, Legionella species, and Chlamydia pneumoniae. Clarithromycin inhibits Mycobacterium avium at concentrations achievable in lung tissue and is active against Borrelia burgdorferi, the cause of Lyme disease. Beta-lactamase production should have no effect on clarithromycin activity. Most strains of methicillin-resistant and oxacillin-resistant staphylcocci are resistant to clarithromycin. Clarithromycin is often combined in drug regimens with at least two other drugs for the treatment of Helicobacter pylori clinical infections; clarithromycin is active against H. pylori in vitro but must be combined with other medications to produce adequate clinical cures and limit the development of resistance. H. pylori resistance to clarithromycin in the US ranges from about 7% to 11%.
Dirithromycin	The spectrum of activity of dirithromycin is comparable to that of erythromycin. Gram-positive organisms susceptible to dirithromycin include penicillin-sensitive Staphylococcus aureus (methicillin-susceptible strains only), Streptococcus pyogenes, S. pneumoniae, and Corynebacterium diphtheriae. Gram-negative coverage is limited, and susceptible gram-negative organisms include Helicobacter jejuni, H. pylori, Moraxella catarrhalis, Bordetella pertussis, B. parapertussis, Legionella pneumophilia, and some strains of Neisseria gonorrhoeae. Dirithromycin is not effective against Listeria spp., H. influenzae, N. gonorrhoeae, or pseudomonas.
Erythromycin	Gram-positive organisms susceptible to erythromycin include Staphylococcus aureus, Streptococcus agalactiae, S. pyogenes, S. pneumoniae, S. viridans group, and Corynebacterium diphtheriae. Gram-negative coverage is limited. In general, erythromycin should not be used against Haemophilus influenzae, although in some cases this organism may be susceptible. Other organisms that have shown susceptibility include Chlamydia trachomatis, Entamoeba histolytica, Listeria monocytogenes, Borrelia burgdorferi (causative agent of Lyme disease), Mycoplasma pneumoniae, Treponema pallidum, and Ureaplasma urealyticum.

III. Comparative Indications of the Single Entity Macrolide Antibiotics[1, 3, 4, 5, 6,

Table 4. FDA-Approved Indications for the Single Entity Macrolide Antibiotics[1, 3, 4, 5, 6]

General Indications For Macrolides				
Indication	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin
Pharyngitis/Tonsillitis	√	√	√	
Respiratory tract infections				√
Acute maxillary sinusitis		√		
Acute bacterial exacerbation of chronic bronchitis		√	√	
Skin and skin structure infections[2]	√	√	√	√
Pertussis (whooping cough)				√
Diphtheria				√
Erythrasma				√
Intestinal amebiasis				√
Uncomplicated urethral, endocervical, or rectal infections				√
Urogenital infections during pregnancy				√
Nongonococcal urethritis				√
Primary syphilis				√
Legionnaire's disease				√
Rheumatic fever				√
Bacterial endocarditis				√
Listeria monocytogenes				√
Pneumonia		√		
Community-acquired pneumonia	√		√	
Disseminated bacterial infections (TWAR strain)		√		
Prevention of disseminated *Mycobacterium avium* complex in patients with advanced HIV infection		√		
Chronic obstructive pulmonary disease	√			
Genital ulcer disease	√			
Pelvic inflammatory disease	√			√
Urethritis/Cervicitis	√			
Secondary bacterial infection of acute bronchitis			√	
Pharyngitis/Tonsillitis	√	√		
Pneumonia		√		
Community-acquired pneumonia	√			
Acute maxillary sinusitis		√		
Acute otitis media	√	√		
Skin and skin structure infections[2]		√		
Disseminated mycobacterial infections		√		

Prevention of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection		√		
Conjunctivitis of the newborn				√
Pneumonia of infancy				√

[1]Causative organisms may vary for each indication for specific macrolides. Refer to individual monographs for this information.
[2]Abscesses usually require surgical drainage.

Prevention of Bacterial Endocarditis[5]

Some macrolides (azithromycin and clarithromycin) have been recommended for prevention of a-hemolytic (viridans group) streptococcal bacterial endocarditis (although not FDA approved) in penicillin-allergic adults and children with congenital heart disease, rheumatic ro other acquired valvular heart dysfunction, prosthetic heart valves, pulmonary shunts or conduits, cardiomyopathy, mitral valve prolapse with valvular regurgitation, previous bacterial endocarditis (even in the absence of heart disease) in patients who undergo dental procedures, and other specific conditions. Erythromycin used to be included in the American Heart Association (AHA) recommendations for prevention of bacterial endocarditis, however, due to adverse events and kinetic parameters, erythromycin is no longer recommended. The AHA does state if physicians have used erythromycin in the past with success in individual patients, erythromycin can continue to be an option in these patients.

IV. Pharmacokinetic Parameters of the Single Entity Macrolide Antibiotics

Table 5. Pharmacokinetic Parameters of the Single Entity Macrolide Antibiotics[1, 3-6]

	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin
Brand Name	Zithromax®, Z-Pak®	Biaxin®, Biaxin® XL	Dynabac®	E-Mycin®, EryPed®, Ery-Tab®, PCE®, various generics
Mechanism of Action[1,3-6]	Inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunit	Inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunit	Inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunit	Inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunit
Pharmacokinetics[1,3-6]				
Bioavailability	38%	50%	10%	>35%
Protein binding	7%-51%	40%-70%	15%-30%	73%-81% (estolate – 96%)
Metabolism	Hepatic (minimal; primarily unchanged)	Hepatic (CYP3A)	Converted by nonezymatic hydrolysis to active moiety (erythromycylamine)	Hepatic
Active Metabolites	None	Yes; 14-OH clarithromycin	Yes; erythromycylamine	None
Elimination	Biliary (94%); renal (6%)	Renal	Fecal/hepatic (97%)	Biliary
Half-Life	68 hours	3-7 hours	2-36 hours (mean: 8)	1.5-2 hours

V. Drug Interactions of the Single Entity Macrolide Antibiotics

Table 6: The most significant drug-drug interactions (Significance Level 1 and 2) for the drugs indexed by Drug Interactions Facts [7]

Drug	Significance	Interaction	Mechanism
Macrolides (Azithromycin, clarithromycin, dirithromycin, and erythromycin)	Level 1	Warfarin Sodium	The total body clearance of WARFARIN is reduced.
Macrolides (Clarithromycin and erythromycin)	Level 1	Carbamazepine	Inhibition of CARBAMAZEPINE (CBZ) hepatic metabolism (CYP3A4), leading to decreased CBZ clearance
Macrolides (Clarithromycin and erythromycin)	Level 1	Cisapride†	Certain MACROLIDE ANTIBIOTICS may inhibit the hepatic metabolism (CYP3A4) of CISAPRIDE..
Macrolides (Clarithromycin and erythromycin)	Level 1	Digoxin	Certain MACROLIDE ANTIBIOTICS may inhibit renal tubular P-glycoprotein excretion of DIGOXIN. Genetic variation in this effect is suspected.
Macrolides (Clarithromycin and erythromycin)	Level 1	Dihydroergotamine, Ergotamine	Although the mechanism is uncertain, it is hypothesized that MACROLIDE ANTIBIOTICS interfere with the hepatic metabolism of ERGOTAMINE.
Macrolides (Azithromycin, clarithromycin, and erythromycin)	Level 1	Atorvastatin, Cerivastatin†, Lovastatin, Simvastatin	Inhibition of metabolism (CYP3A4) is suspected.
Macrolides (Azithromycin, clarithromycin, and erythromycin)	Level 1	Pimozide	MACROLIDE ANTIBIOTICS may inhibit the hepatic metabolism (CYP3A4) of PIMOZIDE.
Macrolides (Erythromycin)	Level 1	Gatifloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin	Unknown.
Macrolides (Clarithromycin and erythromycin)	Level 2	Alprazolam, Diazepam , Midazolam HCl, Triazolam	Decreased metabolism of certain BENZODIAZEPINES.
Macrolides (Clarithromycin and erythromycin)	Level 2	Buspirone	Possibly because of inhibition by a MACROLIDE ANTIBIOTIC of the CYP3A4 isozyme responsible for first-pass metabolism of BUSPIRONE.
Macrolides (Clarithromycin and erythromycin)	Level 2	Cilostazol	Certain MACROLIDE ANTIBIOTICS may inhibit the metabolism (CYP3A4) of CILOSTAZOL.
Macrolides (Clarithromycin and erythromycin)	Level 2	Methylprednisolone	Although this interaction results in an increase in plasma concentrations of METHYLPREDNISOLONE, it is unclear if this alone is responsible for the marked increase in METHYLPREDNISOLONE's effect.
Macrolides (Azithromycin, clarithromycin, and erythromycin)	Level 2	Cyclosporine	MACROLIDE ANTIBIOTICS may interfere with CSA metabolism and may increase rate and extent of absorption or reduce volume of distribution.

Macrolides (Clarithromycin and erythromycin)	Level 2	Grapefruit Juice and Food	FOOD may decrease GI absorption of nonenteric-coated ERYTHROMYCIN base tablets and stearate. GRAPEFRUIT may inhibit the metabolism (CYP3A4) in the small intestine.
Macrolides (Clarithromycin and erythromycin)	Level 2	Repaglinide	Certain MACROLIDE ANTIBIOTICS may inhibit first-pass metabolism (CYP3A4) of REPAGLINIDE.
Macrolides (Clarithromycin and erythromycin)	Level 2	Rifabutin, Rifampin , Rifapentine	RIFAMYCIN metabolism may be inhibited, while MACROLIDE ANTIBIOTIC metabolism may be increased.
Macrolides (Clarithromycin and erythromycin)	Level 2	Tacrolimus	Inhibition of TACROLIMUS hepatic metabolism (CYP3A4).
Macrolides (Azithromycin, clarithromycin, dirithromycin, and erythromycin)	Level 2	Aminophylline, Oxtriphylline, Theophylline	Certain MACROLIDES inhibit the metabolism of THEOPHYLLINE; THEOPHYLLINE reduces the bioavailability and increases renal clearance of oral ERYTHROMYCIN.

† Available from the manufacturer on a limited access protocol.

Additional Drug-Drug Interactions for the Single Entity Macrolide Antibiotics

Macrolide Antibiotic Drug Interactions			
Precipitant Drug	Object Drug*		Description
Antacids	Macrolides Azithromycin Dirithromycin Erythromycin	↔	Aluminum- and magnesium-containing antacids reduce peak serum levels but not the extent of azithromycin absorption. When given immediately following antacids, dirithromycin absorption is slightly enhanced. When given immediately prior to antacids, the elimination rate constant of erythromycin may be slightly decreased.
Fluconazole	Macrolides Clarithromycin	↑	Co-administration led to increases in mean steady-state trough levels (33%) and AUC (18%) of clarithromycin.
H_2 antagonists	Macrolides Dirithromycin	↑	When given immediately after H_2 antagonists, dirithromycin absorption is slightly enhanced.
Macrolides Clarithromycin	Ranitidine bismuth citrate	↔	Co-administration resulted in increased plasma ranitidine levels (57%), increased plasma bismuth trough concentrations (48%), and increased 14-OH clarithromycin plasma levels(31%). These effects do not appear to be clinically important.
Ranitidine bismuth citrate	Macrolides Clarithromycin		
Pimozide	Macrolides Azithromycin Clarithromycin Dirithromycin Erythromycin	↑	Co-administration is contraindicated. Two sudden deaths have occurred when clarithromycin was added to ongoing pimozide therapy.
Rifamycins Rifabutin Rifampin	Macrolides Clarithromycin Erythromycin Troleandomycin	↓	The antimicrobial effects of the macrolide antibiotic may be decreased while the frequency of GI adverse effects may be increased.
Macrolides Erythromycin	Alfentanil	↑	Alfentanil clearance may be decreased and the elimination half-life increased.
Macrolides Clarithromycin Erythromycin	Anticoagulants, oral	↑	Anticoagulant effects may be potentiated. Until more data are available, it is prudent to monitor anticoagulant function in patients receiving anticoagulants and any macrolide antibiotic.
Macrolides Clarithromycin Erythromycin Troleandomycin	Benzodiazepines Alprazolam Diazepam Midazolam Triazolam	↑	The plasma levels of certain benzodiazepines may be elevated, increasing and prolonging the CNS depressant effects. Azithromycin and dirithromycin would not be expected to interact.

Macrolides Erythromycin	Bromocriptine	↑	Bromocriptine serum levels may be elevated, resulting in an increase in the pharmacologic and adverse effects.
Macrolides Clarithromycin Erythromycin Troleandomycin	Buspirone	↑	Plasma buspirone concentrations may be elevated, increasing the pharmacologic and adverse effects. Azithromycin and dirithromycin would not be expected to interact.
Macrolides Clarithromycin Erythromycin Troleandomycin	Carbamazepine	↑	Increased concentrations of carbamazepine may occur. Azithromycin and dirithromycin would not be expected to interact.
Macrolides Clarithromycin Erythromycin Troleandomycin	Cisapride	↑	Co-administration of these drugs is contraindicated. Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT interval prolongation may occur. Azithromycin and dirithromycin would not be expected to interact with cisapride.
Macrolides Azithromycin Clarithromycin Erythromycin Troleandomycin	Cyclosporine	↑	Elevated cyclosporine concentrations with increased risk of toxicity (nephrotoxicity, neurotoxicity) may occur. Azithromycin and dirithromycin would not be expected to interact. However, a single case report implied that azithromycin may interact with cyclosporine.
Macrolides Clarithromycin Erythromycin	Digoxin	↑	Serum digoxin concentrations may be elevated because of the effect of the antibiotic on gut flora that metabolizes digoxin in ≈10% of patients. Carefully monitor patients receiving digoxin and any macrolide antibiotic.
Macrolides Clarithromycin Erythromycin	Disopyramide	↑	Disopyramide plasma levels may be increased. Arrhythmias and increased QT_c intervals have occurred.
Macrolides Clarithromycin Erythromycin Troleandomycin	Ergot alkaloids	↑	Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has occurred. Carefully monitor patients receiving ergot alkaloids and any macrolide antibiotic.
Macrolides Erythromycin	Felodipine	↑	Felodipine plasma levels may be elevated, increasing pharmacologic and adverse effects.
Macrolides Erythromycin	Fluoroquinolones Grepafloxacin Sparfloxacin	↑	Sparfloxacin is contraindicated with erythromycin while grepafloxacin is contraindicated unless appropriate cardiac monitoring can be ensured (e.g., hospitalized patients). Risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased with co-administration.
Macrolides Azithromycin Clarithromycin Erythromycin	HMG-CoA reductase inhibitors	↑	The risk of severe myopathy or rhabdomyolysis may be increased.
Macrolides Erythromycin	Lincosamides	↓	Under some conditions, co-administration may be antagonistic.
Macrolides Erythromycin Troleandomycin	Methylprednisolone	↑	The clearance of methylprednisolone is greatly reduced. This has been used as a therapeutic advantage to reduce the dose.
Macrolides Clarithromycin	Omeprazole	↑	Co-administration may result in increased plasma levels of omeprazole, clarithromycin, and 14-OH clarithromycin.
Omeprazole	Macrolides Clarithromycin		
Macrolides Troleandomycin	Oral contraceptives	↑	Concurrent use may result in increased risk of intrahepatic cholestasis caused by decreased metabolism and accumulation of the contraceptive.
Macrolides Erythromycin	Penicillins	↔	Both antagonism and synergism have occurred with co-administration.
Macrolides Clarithromycin Erythromycin Troleandomycin	Tacrolimus	↑	Concurrent use may be associated with elevated serum tacrolimus levels, increasing the risk of side effects (e.g., nephrotoxicity). Azithromycin and dirithromycin would not be expected to interact.

Macrolides Clarithromycin Erythromycin Troleandomycin	Theophylline	↑	Concurrent use may be associated with increased serum theophylline levels. Azithromycin and dirithromycin would not be expected to interact. Monitor serum theophylline levels in patients receiving theophylline and any macrolide antibiotic. In addition, plasma erythromycin levels may be decreased.
Theophylline	Macrolides Erythromycin	↓	
Macrolides Erythromycin	Vinblastine	↑	Risk of vinblastine toxicity (e.g., constipation, myalgia, neutropenia) may be increased.
Macrolides Clarithromycin	Zidovudine	↔	Peak serum zidovudine concentrations may be increased or decreased.

↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.

VI. Adverse Drug Events of the Single Entity Macrolide Antibiotics

Table 7. Common Adverse Events (%) Reported for the Single Entity Macrolide Antibiotics[6,8]

Macrolide Adverse Reactions (> 1%)				
Adverse reaction	**Azithromycin**	**Clarithromycin**	**Dirithromycin**	**Erythromycin**
GI				
Abdominal pain/ discomfort	1.9-7	2	9.7	7.5
Abnormal taste	--	3	> 0.1 - < 1	--
Anorexia	1.9	--	> 0.1 - < 1	√
Diarrhea/loose stools	4.3-14	3	7.7	7.3
Dyspepsia	= 1	2	2.6	2.1
Flatulence	= 1	--	1.5	1.5
GI disorder	--	--	1.6	1.4
Nausea	3-18	3	8.3	7.5
Vomiting	= 7	--	3	2.8
Injection site reactions				
Local inflammation	3.1	--	--	--
Pain	6.5	--	--	--
Lab test abnormalities				
ALT elevated	1-6	< 1	> 0.1 - < 1	--
AST elevated	1-6	< 1	> 0.1 - < 1	--
Bicarbonate decreased	--	--	1.4	2
BUN elevated	< 1	4	--	--
Eosinophils increased	--	--	1.2	0.6
GGT elevated	1-2	< 1	> 0.1 - < 1	--
LDH elevated	= 3	< 1	--	--
Platelet count increased	--	--	3.8	4.8
Potassium elevated	1-2	--	2.6	--
Segmented neutrophils increased	--	--	1.2	1.3
Serum CPK elevated	1-2	--	1.2	0.9

Serum creatinine elevated	= 6	< 1	> 0.1 - < 1	--
Total bilirubin elevated	= 3	< 1	> 0.1 - < 1	--
Miscellaneous				
Asthenia	--	--	2	1.9
Dizziness	= 1	--	2.3	2.3
Dyspnea	--	--	1.2	1.2
Headache	= 1	2	8.6	8.2
Increased cough	--	--	1.5	2.6
Pain (non-specific)	--	--	2.2	1.6
Pruritus	1.9	--	1.2	1
Rash	1.9	--	1.4	2.6
Vaginitis	= 2.8	--	0.4	0.6
Sudden cardiac death[19,20]	--	--	--	√*
Children				
Abdominal pain	1.9-3	3	--	--
Diarrhea/loose stools	2-6	6	--	--
Headache	= 1	2	--	--
Nausea	1-2	--	--	--
Rash	= 1.6	3	--	--
Vomiting	1-5	6	--	--

[19]√ = Event occurred, but incidence is unknown.
* Oral erythromycin in conjunction with CYP3A inhibitors increases the risk of sudden cardiac death.

The following adverse reactions occurred at an incidence unknown or = 1%:[6, 8]

Azithromycin:
Mucositis; oral moniliasis; melena; cholestatic jaundice; gastritis; chest pain; palpitations; fatigue; somnolence; vertigo; monilia; nephritis; angioedema; photosensitivity; bronchospasm; taste perversion; elevated serum alkaline phosphatase; leukopenia; neutropenia; elevated blood glucose; elevated phosphate; decreased platelet count. Laboratory test abnormalities appeared to be reversible.

Children:
Hyperkinesia; dizziness; agitation; nervousness; insomnia; fatigue; fever; malaise; dyspepsia; constipation; anorexia; flatulence; gastritis; conjunctivitis; chest pain; pruritus; urticaria.

Significant abnormalities occurring in children during clinical trials were reported at a frequency of <1% but were similar in type to the adult pattern.

Clarithromycin:
Elevated alkaline phosphatase; elevated prothrombin time; decreased WBC.

Dirithromycin:
Abnormal stools; constipation; gastritis; anorexia; dry mouth; dysphagia; gastroenteritis; mouth ulceration; palpitations; anxiety; depression; nervousness; paresthesias; somnolence; peripheral edema; sweating; syncope; thirst; tinnitus; tremor; vasodilation; dysmenorrhea; urinary frequency; vaginal moniliasis; allergic reaction; amblyopia; dehydration; edema; epistaxis; eye disorder; fever; flu syndrome; hemoptysis; hyperventilation; malaise; myalgia; myasthenia; neck pain; insomnia; increased leukocytes; elevated alkaline phosphatase; decreased platelet count; decreased albumin; decreased chloride; decreased hematocrit; decreased hemoglobin; decreased lymphocytes; decreased segmented neutrophils; decreased phosphorus; decreased serum alkaline

phosphatase; decreased serum uric acid; decreased total protein; increased basophils ; increased calcium; increased lymphocytes; increased hematocrit; increased hemoglobin; increased monocytes; increased phosphorus; increased uric acid.

Erythromycin:
Pseudomembranous colitis; anorexia; ventricular arrhythmias; hepatotoxicity; urticaria; bullous eruptions; eczema; erythema multiforme; Stevens-Johnson syndrome; toxic epidermal necrolysis; allergic reaction; anaphylaxis; insomnia; increased leukocytes.

Local:
Venous irritation and phlebitis have occurred with parenteral administration of erythromycin, but the risk of such reactions may be reduced if the infusion is given slowly, in dilute solution, by continuous IV infusion, or intermittent infusion over 20 to 60 minutes.

Special senses:
There have been isolated reports of reversible hearing loss with erythromycin occurring chiefly in patients with renal or hepatic insufficiency, in the elderly, and in those receiving high doses (>4g/day). In rare instances involving IV use, the ototoxic effect has been irreversible.

VII. Dosing and Administration for the Single Entity Macrolide Antibiotics

Table 8A. Usual Dosing for the Single Entity Macrolide Antibiotics

	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin
Usual Adult Dose[1,3-6]	500mg single dose on day one, then 250mg QD days 2-5. Single 1-2g dose	500-100mg/day x 7-14 days	500mg QD x 5-14 days	1000mg/day in divided doses x 7-21 days (max: 4g/day)
Usual Pediatric Dose[1,3-6]	10-30mg/kg x 1-3 days 10mg/kg day 1, then 5mg/kg days 2-5	7.5mg/kg/d q12h x 10days	Not indicated for patients less than 12 years of age	30-50mg/kg/day in divided doses x 7-21 days
Availability[1,3-6]	• Oral suspension: 100mg/5ml, 200mg/5ml • Powder packet: 1g • Tablets: 250mg, 500mg, 600mg	• Oral suspension: 125mg/5ml, 250mg/5ml • Tablets: 250mg, 500mg • Tablets, extended release: 500 mg	• Tablets: 250mg	• Capsules, delayed release: 250mg • Powder for suspension: 200mg/5ml, 400mg/5ml • Suspension: 100mg/2.5ml, 125mg/5ml, 200mg/5ml, 250mg/5ml, 400mg/5ml • Tablets: 400mg • Tablets, chewable: 200mg • Tablets, enteric coated: 250mg, 333mg, 500mg • Tablets, film coated: 250mg, 500mg • Tablets, polymer coated particles: 333mg, 500mg

Table 8B. Dosing for the Single Entity Macrolide Antibiotics[6, 8]

<table>
<tr><th>Drug</th><th>Availability</th><th>Dose/Frequency/Duration</th></tr>
<tr><td>Azithromycin</td><td>Tablets:
250mg (as dihydrate)
500mg (as dihydrate)
600mg (as dihydrate)

Powder for Injection, lyophilized: 500mg

Powder for Oral Suspension:
100mg/5mL
200mg/5mL
1g/packet (as dihydrate)</td><td>Oral:
Adults:
Mild to moderate acute bacterial exacerbations of COPD in patients 16 years of age and older:
500mg/day for 3 days or 500mg as a single dose on the first day followed by 250mg once daily on days 2 through 5.

Community-acquired pneumonia of mild severity, pharyngitis/tonsillitis(as second-line therapy), and uncomplicated skin and skin structure infections in patients 16 years of age and older:
500mg as a single dose on the first day followed by 250mg once daily on days 2 through 5.

Genital ulcer disease caused by H. ducreyi (chancroid):
Single 1g dose.

Nongonococcal urethritis/cervicitis caused by C. trachomatis:
Single 1g dose.

Gonococcal urethritis/cervicitis caused by N. gonorrhoeae:
Single 2g dose.

Prevention of disseminated MAC infections:
1200mg taken once weekly. This dose of azithromycin may be combined with the approved dosage regimen of rifabutin.

Treatment of disseminated MAC infections:
Take 600mg/day in combination with ethambutol at the recommended daily dose of 15mg/kg. Other antimycobacterial drugs that have shown in vitro activity against MAC may be added to the regimen of azithromycin plus ethambutol at the discretion of the physician or health care provider.

Prevention of bacterial endocarditis (non-FDA approved indication):
A single 500mg (adults) dose should be given 1 hour prior to the procedure. Children should receive a dose of 15mg/kg. This is the American Heart Association Recommendation.

Children:
Acute otitis media:
30mg/kg oral suspension given as a single dose or 10mg/kg once daily for 3 days or 10mg/kg as a single dose on the first day, followed by 5mg/kg on days 2 through 5.

Community-acquired pneumonia:
10mg/kg oral susp. as a single dose on the first day followed by 5mg/kg on days 2 through 5.

<table>
<tr><th colspan="8">Azithromycin Pediatric Dosage Guidelines for Otitis Media and Community-Acquired Pneumonia(= 6 months of age) 5-Day Regimen[1, 2]</th></tr>
<tr><th colspan="2">Weight</th><th colspan="2">Amount of 100mg/5mL suspension</th><th colspan="2">Amount of 200mg/5mL suspension</th><th rowspan="2">Total mL per treatment course</th><th rowspan="2">Total mg per treatment course</th></tr>
<tr><th>kg</th><th>lbs</th><th>Day 1</th><th>Days 2 to 5</th><th>Day 1</th><th>Days 2 to 5</th></tr>
<tr><td>5</td><td>11</td><td>2.5mL</td><td>1.25mL</td><td></td><td></td><td>7.5mL</td><td>150mg</td></tr>
<tr><td>10</td><td>22</td><td>5mL</td><td>2.5mL</td><td></td><td></td><td>15mL</td><td>300mg</td></tr>
<tr><td>20</td><td>44</td><td></td><td></td><td>5mL</td><td>2.5mL</td><td>15mL</td><td>600mg</td></tr>
<tr><td>30</td><td>66</td><td></td><td></td><td>7.5mL</td><td>3.75mL</td><td>22.5mL</td><td>900mg</td></tr>
<tr><td>40</td><td>88</td><td></td><td></td><td>10mL</td><td>5mL</td><td>30mL</td><td>1200mg</td></tr>
<tr><td>= 50</td><td>= 110</td><td></td><td></td><td>12.5mL</td><td>6.25mL</td><td>37.5mL</td><td>1500mg</td></tr>
</table>
1 Dosing calculated on 10mg/kg on day 1, followed by 5mg/kg on days 2 to 5.
2 Effectiveness of 1- or 3-day regimen in children with community-acquired pneumonia has not been established.</td></tr>
</table>

Azithromycin (Continued)

Azithromycin Pediatric Dosage Guidelines for Otitis Media: 3-Day Regimen[1]					
Weight		Amount of 100mg/5mL suspension	Amount of 200mg/5mL suspension	Total mL per treatment course	Total mg per treatment course
Kg	Lbs	Day 1 to 3	Day 1 to 3		
5	11	2.5mL		7.5mL	150mg
10	22	5mL		15mL	300mg
20	44		5mL	15mL	600mg
30	66		7.5mL	22.5mL	900mg
40	88		10mL	30mL	1200mg
= 50	= 110		12.5mL	37.5mL	1500mg

1 Dosing calculated on 10mg/kg/day.

Azithromycin Pediatric Dosage Guidelines for Otitis Media: 1-Day Regimen[1]				
Weight		Amount of 200mg/5mL suspension	Total mL per treatment course	Total mg per treatment course
Kg	lbs	Day 1		
5	11	3.75mL	3.75mL	150mg
10	22	7.5mL	7.5mL	300mg
20	44	15mL	15mL	600mg
30	66	22.5mL	22.5mL	900mg
40	88	30mL	30mL	1200mg
= 50	= 110	37.5mL	37.5mL	1500mg

1 Dosing calculated on 30mg/kg as a single dose.

Pharyngitis/Tonsillitis:
12mg/kg once daily for 5 days. See the following table.

Azithromycin Pediatric Dosage Guidelines for Pharyngitis/Tonsillitis: 5-Day Regimen (= 2 years of age)[1]				
Weight		Amount of 200 mg/5 mL suspension	Total mL per treatment course	Total mg per treatment course
Kg	lbs	Day 1 to 5		
8	18	2.5mL	12.5mL	500mg
17	37	5mL	25mL	1000mg
25	55	7.5mL	37.5mL	1500mg
33	73	10mL	50mL	2000mg
40	88	12.5mL	62.5mL	2500mg

1 Dosing calculated on 12mg/kg/day for 5 days.

IV:
Adults:
Infuse injections over a period of = 60 minutes. The infusate concentration and rate of infusion for azithromycin for injection should be 1mg/mL over 3 hours or 2mg/mL over 1 hour. Do not administer azithromycin for injection as a bolus or IM injection.

Community-acquired pneumonia:
500mg as a single daily dose IV for = 2 days. Follow IV therapy by the oral route at a single daily dose of 500mg to complete a 7- to 10-day course of therapy.

Pelvic inflammatory disease:
500mg as a single daily dose IV for 1 or 2 days. Follow IV therapy by the oral route at a single daily dose of 250mg to complete a 7-day course of therapy. If anaerobic microorganisms are suspected in infection, administer an agent with anaerobic activity with azithromycin.

Clarithromycin

Tablets:
250mg
500mg

Granules for oral suspension when reconstituted:
125mg/5mL
250mg/5mL

Tablets, extended-release:
500mg

Adults:

Clarithromycin Dosage Guidelines				
	Tablets		Extended-release tablets	
Infection	Dosage (q 12 hr)	Duration (days)	Dosage (q 24 hr)	Duration (days)
Pharyngitis/Tonsillitis	250mg	10	-	-
Acute maxillary sinusitis	500mg	14	2 × 500mg	14
Acute exacerbation of chronic bronchitis caused by:				
H. parainfluenzae	500mg	7	2 × 500mg	7
S. pneumoniae	250mg	7 to 14	2 × 500mg	7
M. catarrhalis	250mg	7 to 14	2 × 500mg	7
H. influenzae	500mg	7 to 14	2 × 500mg	7
Community-acquired pneumonia caused by:				
S. pneumoniae	250mg	7 to 14	2 × 500mg	7
M. pneumoniae	250mg	7 to 14	2 × 500mg	7
H. influenzae	250mg	7	2 × 500mg	7
H. parainfluenzae	-	-	2 × 500mg	7
M. catarrhalis	-	-	2 × 500mg	7
C. pneumoniae	250mg	7 to 14	2 × 500mg	7
Uncomplicated skin and skin structure infection	250mg	7 to 14	-	-

***H. pylori* eradication to reduce the risk of duodenal ulcer recurrence:**
Triple therapy:
Clarithromycin/Lansoprazole/Amoxicillin:
500mg clarithromycin, 30mg lansoprazole, and 1g amoxicillin every 12 hours for 10 or 14 days.

Clarithromycin/Omeprazole/Amoxicillin:
500mg clarithromycin, 20mg omeprazole, and 1g amoxicillin every 12 hours for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy:
Clarithromycin/Omeprazole:
500mg clarithromycin 3 times/day (every 8 hours), and 40mg omeprazole once daily (every morning) for 14 days. An additional 14 days of 20mg omeprazole once daily is recommended for ulcer healing and symptom relief.

Clarithromycin/Ranitidine bismuth citrate:
500mg clarithromycin 2 times/day (every 12 hours) or 3 times/day(every 8 hours), and 400mg ranitidine bismuth citrate given 2 times/day (every 12 hours) for 14 days. An additional 14 days of ranitidine bismuth citrate 2 times/day is recommended for ulcer healing and symptom relief. This combination is not recommended in patients with a creatinine clearance < 25mL/min.

Mycobacterial infections:
Recommended as the primary agent for the treatment of disseminated MAC. Use in combination with other antimycobacterial drugs that have shown in vitro activity against MAC or clinical benefit in MAC treatment. Continue clarithromycin therapy for life if clinical and mycobacterial improvements are observed.

Dosage (treatment and prevention):
Adults:
500mg twice daily.

Clarithromycin (continued)

Prevention of bacterial endocarditis (non-FDA approved indication):
A single 500mg dose (adults) should be given 1 hour prior to the procedure. Children should receive a dose of 15mg/kg. This is the American Heart Association Recommendation.

Children:
7.5mg/kg twice daily up to 500mg twice daily. Doses recommended for pediatric prophylaxis are derived from MAC treatment studies in children. Refer to the Pediatric Dosage table for dosing recommendations.

Children:
Usual recommended daily dosage is 15mg/kg/day divided every 12 hours for 10 days.

Pediatric Clarithromycin Dosage Guidelines (Based on Body Weight)

Dosing calculated on 7.5 mg/kg q 12 hr

Weight		Dose (q 12 hr)	125mg/5mL (q 12 hr)	250mg/5mL (q 12 hr)
Kg	lbs			
9	20	62.5mg	2.5mL	1.25mL
17	37	125mg	5mL	2.5mL
25	55	187.5mg	7.5mL	3.75mL
33	73	250mg	10mL	5mL

Erythromycin

Capsules, delayed release:
250mg

Powder for suspension:
200mg/5ml
400mg/5ml

Suspension:
100mg/2.5ml
125mg/5ml
200mg/5ml
250mg/5ml
400mg/5ml

Tablets:
400mg

Tablets, chewable:
200mg

Tablets, enteric coated:
250mg
333mg
500mg

Tablets, film coated:
250mg
500mg

Tablets, polymer coated particles:
333mg
500mg

Oral:
Dosages and product strengths are expressed as erythromycin base equivalents. Because of differences in absorption and biotransformation, varying quantities of each salt form are required to produce the same free erythromycin serum levels. For example, expressed in base equivalents, 400mg erythromycin ethylsuccinate produces the same free erythromycin serum levels as 250mg of erythromycin base, stearate, or estolate.

Optimal serum levels of erythromycin are reached when erythromycin base or stearate is taken in the fasting state or immediately before meals. Erythromycin ethylsuccinate, estolate, and enteric-coated erythromycin may be administered without regard to meals.

Urine alkalinization (pH 8.5) increases erythromycin's gram-negative antibacterial activity; several investigators suggest co-administration of urinary alkalinizers (e.g., sodium bicarbonate) and erythromycin for urinary tract infections.

Usual dosage:
Adults:
250mg (or 400mg ethylsuccinate) every 6 hours taken 1 hour before meals, or 500mg every 12 hours, or 333mg every 8 hours. May increase up to 4g/day, according to severity of infection. If twice daily dosage is desired, the recommended dose is 500mg every 12 hours. Twice daily dosing is not recommended when doses >1g/day are administered.

Children:
30 to 50mg/kg/day (15 to 25mg/lb/day) in divided doses. Proper dosage is determined by age, weight, and severity of infection. When twice daily dosing is desired, half of the total daily dose may be taken every 12 hours. For more severe infections, dosage may be doubled.

Erythromycin Uses and Dosages

Indication (Organism)	Dosage (Stated as erythromycin base)
Labeled uses:	
Upper respiratory tract infections of mild to moderate severity	
S. pyogenes (group A beta-hemolytic streptococcus)	250 to 500mg 4 times/day or 20 to 50mg/kg/day for children (not to exceed the adult dose) in divided doses for 10 days.
S. pneumoniae	250 to 500mg every 6 hours.
H. influenzae (used concomitantly with a sulfonamide)	Erythromycin ethylsuccinate:50mg/kg/day for children (not to exceed 6g/day). Sulfisoxazole: 150mg/kg/day. Combination given for 10 days.
Lower respiratory tract infections of mild to moderate severity	
S. pyogenes (group A beta-hemolytic streptococcus)	250 to 500mg 4 times/day or 20 to 50mg/kg/day for children (not to exceed the adult dose) in divided doses for 10 days.
S. pneumoniae	250 to 500mg every 6 hours.
Respiratory tract infections	
M. pneumoniae (Eaton agent, PPLO)	500mg every 6 hours for 5 to 10 days. Treat severe infections for up to 3 weeks.
Skin and skin structure infections of mild to moderate severity	
S. pyogenes	250 to 500mg 4 times/day or 20 to 50mg/kg/day for children (not to exceed the adult dose) in divided doses for 10 days.
S. aureus (resistant organisms may emerge)	250mg every 6 hours or 500mg every 12 hours, maximum 4g/day.
Pertussis (whooping cough)	

Erythromycin (continued)

B. pertussis:Effective in eliminating the organism from the nasopharynx of infected patients. May be helpful in prophylaxis of pertussis in exposed individuals.	40 to 50mg/kg/day for children (not to exceed the adult dose) in divided doses for 5 to 14 days, or 500mg 4 times/day for 10 days.
Diphtheria	
C. diphtheriae:Adjunct to antitoxin to prevent establishment of carriers and to eradicate organism in carriers.	500mg every 6 hours for 10 days.
Erythrasma	
C. minutissimum	250mg 3 times/day for 21 days.
Intestinal amebiasis	
E. histolytica:Oral erythromycin only.	Adults: 250mg 4 times/day for 10 to 14 days. Children: 30 to 50mg/kg/day in divided doses for 10 to 14 days.
Pelvic inflammatory disease(PID), acute	
N. gonorrhoeae: Erythromycin lactobionate IV followed by oral erythromycin.[1]	500mg IV every 6 hours for 3 days, then 250mg orally every 6 hours for 7 days.
Conjunctivitis of the newborn, pneumonia of infancy, urogenital infections during pregnancy *C. trachomatis*	50mg/kg/day for children (not to exceed the adult dose) in 4 divided doses for 10 to =14 days (conjunctivitis) or = 21 days (pneumonia); 500mg 4 times daily for 7 days or 250mg 4 times daily on an empty stomach for = 14 days (urogenital infections).
Urethral, endocervical, or rectal infections, uncomplicated	
C. trachomatis[1]	500mg = 4 times/day for 7 days or 250mg 4 times/day for 14 days if patient cannot tolerate high-dose erythromycin.[2]
Nongonococcal urethritis	
U. urealyticum[1]	500mg 4 times/day for at least 7 days or 250mg orally 4 times/day for 14 days if patient cannot tolerate high-dose erythromycin.[2]
Primary syphilis	
T. pallidum:Oral only[1]	20 to 40g in divided doses over 10 to 15 days.
Legionnaire's disease	
L. pneumophila:No controlled clinical efficacy studies have been conducted, but data suggest effectiveness	1 to 4g/day in divided doses for 10 to 14 days.
Rheumatic fever	
S. pyogenes (group A beta-hemolytic streptococci): Prevention of initial or recurrent attacks.[1]	250mg 2 times daily.
Bacterial endocarditis (in penicillin-allergic patients with valvular heart disease who are to undergo dental procedures or surgical procedures of the upper respiratory tract).	
Alpha-hemolytic streptococcus (viridans)[1]	Adults: 1g, 1 to 2 hours prior to procedure, then 500mg 6 hours after initial dose.[3] Children:20mg/kg, 2 hours prior to procedure, then 10mg/kg, 6 hours after initial dose.[3]
Listeria monocytogenes	Adults: 250mg every 6 hours or 500mg every 12 hours, maximum 4g/day.

[1]Use as alternative drug in penicillin or tetracycline hypersensitivity or when penicillin or tetracycline are contraindicated or not tolerated.
[2]CDC 1998 Guidelines for Sexually Transmitted Diseases Treatment. *Morbidity and Mortality Weekly Report* 1998 Jan 23;47(No. 441):1-117.
[3]American Heart Association statement. *JAMA* 1990;264:2919-2922.
[4]Use as alternate therapy to trimethoprim-sulfamethoxazole or doxycycline.

Dirithromycin	**Tablets, delayed release:** 250mg	Recommended Dosage Schedule for Dirithromycin (= 12 years of age)

Infection (mild to moderate severity)	Dose	Frequency	Duration (days)
Acute bacterial exacerbations of chronic bronchitis caused by *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae*.	500mg	once a day	5 to 7
Secondary bacterial infection of acute bronchitis caused by *M. catarrhalis* or *S. pneumoniae*.	500mg	once a day	7
Community-acquired pneumonia caused by *L. pneumophila*, *M. pneumoniae*, or *S. pneumoniae*.	500mg	once a day	14
Pharyngitis/tonsillitis caused by *S. pyogenes*.	500mg	once a day	10
Uncomplicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible) or *S. pyogenes*.	500mg	once a day	5 to 7

Special Dosing Considerations

Table 9. Special Dosing Considerations for the Single Entity Macrolide Antibiotics[1,3-6]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed/Stability
Azithromycin	No dosage adjustment is recommended for subjects with renal impairment.	-	Yes **Note:** Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, nosocomially acquired infections, known or suspected bacteremia, patients requiring hospitalization, or those with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).	B	**Tablets:** Store tablets between 15° to 30°C (59° to 86°F). **Oral suspension:** Store dry powder below 30°C (86°F). Store single-dose packets between 5° and 30°C (41° and 86°F). Store reconstituted oral suspension between 5° and 30°C (41° and 86°F)and use within 10 days. Discard after full dosing is completed. **IV:** Diluted solution for injection is stable for 24 hours when stored = 30°C or 86°F or for 7 days refrigerated at 5°C (41°F).
Clarithromycin	May be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. In the presence of	Refer to renal dosing	Yes	C (Clarithromycin has demonstrated adverse effects on pregnancy)	**Tablets and granules:** Store at controlled room temperature in a well-closed container. Protect the 250mg tablets from light. **Extended-release tablets:** Store the extended-release tablets at 20° to 25°C (68° to 77°F); excursions permitted to

	severe renal impairment (Ccr < 30mL/min) with or without coexisting hepatic impairment, halve the dose or double the dosing interval				15° to 30°C (59° to 86°F). **Reconstituted suspension:** Shake well before each use. Keep tightly closed. Do not refrigerate. After mixing, store at 15° to 30°C (59° to 86°F), and use within 14 days.
Dirithromycin	No adjustment necessary	Do not use in patients with moderate or severe hepatic impairment	Safety and efficacy has not been established in patients less than 12 years of age.	C (Dirithromycin has demonstrated teratogenic effects in animals)	Store at controlled room temperature 15° to 30°C (59° to 86°F).
Erythromycin	No adjustments necessary.	-	Yes	B (Erythromycin crosses the placental barrier, but fetal levels are low)	**IV:** The *initial* solution is stable for 2 weeks if refrigerated or for 24 hours at room temperature. Completely administer the final diluted solution within 8 hours in order to ensure proper potency because it is not suitable for storage. Use the solution in the piggyback vial within 8 hours if stored at room temperature and 24 hours if stored in the refrigerator. If the solution is to be frozen, freeze at -10° to -20°C (14° to -4°F) within 4 hours of preparation. Frozen solution may be stored for 30 days. Thaw the frozen solution in the refrigerator and use within 8 hours after thawing is completed. Thawed solution must not be refrozen.

VIII. Comparative Effectiveness of the Single Entity Macrolide Antibiotics

Table 10 describes published, peer-reviewed trials of the drugs within this class.

Table 10. Additional Outcomes Evidence for the Single Entity Macrolide antibiotics

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Upper respiratory tract infections						
Arguedas A, et al.[9]	Randomized, open clinical trial	• Age 6 months – 12 years • Acute otitis media with effusion	n=100	• Azithromycin 10mg/kg QD x 3d • Clarithromycin 15mg/kg/d in 2 divided doses x 10d	10 days (60 day follow-up)	**Efficacy: azithromycin » clarithromycin** • 97 patients were considered evaluable. • Most common pathogens: *Steptococcus pneumoniae* (60%), *Haemophilus influenzae* (15%), *Staphylococcus aureus* (13%) • 50 (100%) azithromycin patients and 45 (95.7%) clarithromycin patients achieved a satisfactory clinical response. • Rates of persistence of middle ear effusion were comparable. **Safety: azithromycin » clarithromycin** • Rates of possible drug-related side effects were comparable.
Venuta A, et al.[10]	Randomized, observer-blind trial	• Children • Documented *Streptococcus pyogenes* pharyngitis	n=174	• Azithromycin 10mg/kg QD x 3d • Clarithromycin 7.5mg/kg/d BID x 10d	10 days	**Efficacy: azithromycin » clarithromycin** • The observed cure rate 10 days after the beginning of treatment was 96.8% (61) in the clarithromycin group and 95.9% (71) in the azithromycin group. • At days 17-20 the bacteriological eradication rate was 95.2% for clarithromycin and 94.6% for azithromycin. • When children who did not complete treatment were included in the analysis, the eradication rates were statistically higher for azithromycin (93.6% vs. 82.9%; $p<0.05$) due to better compliance with the azithromycin regimen.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Lower respiratory tract infections						
O'Doherty B, Muller O[11]	Randomized, multicenter	• Adults • Mild to moderate community-acquired pneumonia (CAP)	n=203	• Azithromycin 500mg QD x 3d • Clarithromycin 250mg BID x 10d	10 days (16-23 day follow up)	**Efficacy: azithromycin » clarithromycin** • 94% (83) of evaluable azithromycin patients and 95% (84) of evaluable clarithromycin patients achieved a satisfactory clinical response at the end of therapy. • At days 19-23, only one patient in each treatment group had relapsed. • All atypical pneumonias had a satisfactory clinical response. **Safety: azithromycin » clarithromycin** • The incidences of treatment-related adverse events were similar for the two groups. • Two clarithromycin patients discontinued due to severe treatment related events.
Wubbel L, et al.[12]	Randomized	• Previously healthy • Age 6 months to 16 years • Tachypnea, fever, cough or rales and an abnormal chest X-ray consistent with CAP	n=168	• Azithromycin 10mg/kg on Day 1, then 5mg/kg QD x 4d • Amoxicillin-clavulanate 40mg/kg/d in 3 divided doses x 10d in those <5 • Erythromycin estolate 40mg/kg/d in 3 divided doses x 10 in those >5	10 days (10-37 day follow up)	**Efficacy: azithromycin » amoxicillin/clavulanate » erythromycin estolate** • Etiology was established in 73 (43%) of patients. Identified pathogens were *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae* and viruses. 15 patients were coinfected. • Bacteriologic response: all patients with *Mycoplasma* pneumonia reached clinical cure after treatment, as did all *Chlamydia* patients. • Of the 147 clinically evaluable patients, 143 were classified as clinical cure. There were no differences in effectiveness of the different therapies. **Safety: azithromycin ³ erythromycin estolate > amoxicillin-clavulanate** • 11 patients did not complete the prescribed therapy – 4 due to adverse events, the remaining 7 at various times for inexplicable reasons. • Adverse event rates: amoxicillin-clavulanate 67% (33/49 patients) – diarrhea (20 patients), genital candidiasis (6), rash (4), abdominal pain (2), vomiting (1); erythromycin 25% (8/29) – diarrhea (2), headache (2), vomiting (1), rash (10, nausea (1), swollen face (1); azithromycin 14% (10/69) – diarrhea (3), rash (3), abdominal pain (2), vomiting (1), oral thrush (1)

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Cazzola M, et al.[13]	Not described	• Outpatients • Stage III (Ball's stratification) acute bacterial exacerbation of chronic bronchitis	n=80	• Dirithromycin 500mg QD x 5d • Azithromycin 500mg QD x 3d	5 days	**Efficacy: dirithromycin » azithromycin** • Primary pathogens: *S. pneumoniae, H. influenzae, M. catarrhalis* • Post-therapy eradication rates: dirithromycin 90% (36/40), azithromycin 92.5% (37/40) • Persistence of H. influenzae isolates: dirithromycin 27.3% (3/11), azithromycin 22.2% (2/9) • Post-therapy treatment success (cure or improvement): dirithromycin 90% (36/40), azithromycin 92.5% (37/40) **Safety: dirithromycin » azithromycin** • Incidence of side effects: dirithromycin 10%, azithromycin 12.5% • Most common side effects: abdominal cramps, nausea, diarrhea, other GI complaints
Wasilewski MM, Johns D, Sides GD[14]	Meta-analysis (2 randomized, double-blind trials)	• ≥ 12 years old • Acute exacerbation of chronic bronchitis • ≥ 37kg • Able to swallow tablets • Negative pregnancy test • Adequate birth control (women)	n=1057	• Dirithromycin 500mg QD x 5d • Erythromycin 250mg q6h x 7d • Dummy tablets were used to blind the regimens	7 days (14 day follow up)	**Efficacy: dirithromycin » erythromycin** • Clinical efficacy: dirithromycin was equivalent to erythromycin in all measures of clinical response at post-therapy (80% vs. 78.7%) and at termination (74% vs. 71.5%) {intent-to-treat group}. • Bacteriological efficacy: the microbiological cure rates were equivalent at post therapy (47.8% vs. 48.5%) and at termination (46.3% vs. 45.2%) {intent-to-treat group}. Dirithromycin was as effective as erythromycin in eradicating *S. pneumoniae, H. influenzae, M. catarrhalis* and *S. aureus.* • Dirithromycin patients were statistically significantly more compliant than erythromycin patients (97.8% vs. 86.9%, p<0.001). **Safety: dirithromycin » erythromycin** • There were no statistically significant differences in the number of patients reporting at least one adverse event or in those reporting individual adverse events. • The most common adverse events for both treatments were headache, abdominal pain, diarrhea, and nausea.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Hosie J, et al.[15]	Randomized, single-blind, multicenter	• Acute bacterial exacerbation of chronic bronchitis	n=212	• Dirithromycin 500mg QD x 5d • Clarithromycin 250mg BID x 7d	7 days	**Efficacy: dirithromycin » clarithromycin** • Post-therapy favorable clinical response: dirithromycin 89.5%, clarithromycin 94.8% • Post-therapy favorable bacteriological response: dirithromycin 68.8%, clarithromycin 71.9% • These differences were neither statistically nor significantly different. • Both drugs had similar efficacy against *H. influenzae*. **Safety: dirithromycin » clarithromycin** • Both drugs were well tolerated. • Four dirithromycin patients were non-compliant, compared to 12 non-compliant azithromycin patients. This difference was not significant.
Lebel MH, Mehra S[16]	Randomized, single-blind (investigator), parallel group	• Age 1 month to 16 years • Clinical syndrome of pertussis – cough ≥ d and/or one of the following: 1) paroxysmal cough, 2) cough ending in apnea or vomiting, 3) inspiratory whoop	n=153	• Clarithromycin 7.5mg/kg BID x 7d • Erythromycin estolate 13.3mg/kg/dose TID x 14d	14 days	**Efficacy: clarithromycin » erythromycin** • Microbiologic eradication: per protocol (n=54) – clarithromycin 100% (95% CI 88.8-100), erythromycin 96% (95% CI 78.1-99.9); Intent-to-treat (n=62) – clarithromycin 89% (95% CI 73.3-96.8), erythromycin 89% (95% CI 70.8-97.6) • Clinical cure rates: Per protocol – clarithromycin 100%, erythromycin 96%; Intent-to-treat – clarithromycin 94%, erythromycin 89% **Safety: clarithromycin > erythromycin** • No deaths or serious adverse events occurred. • The incidence of treatment-emergent drug-related adverse events was significantly higher with erythromycin (62% vs. 45%, p=0.035). • Three erythromycin patients and one clarithromycin patient discontinued due to adverse events. • The mean percentage of drug taken (among all randomized patients) was 98.5%±9.6% (18-100%) for clarithromycin compared to 88.6%±21.2% (7-100%) for erythromycin (p<0.001).

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Wasilewski MM, et al.[17]	Randomized, double-blind, double-dummy multicenter with 2 parallel arms	• Age ≥ 12 years • Weight ≥ 37kg • Culturable bacterial infection of the skin and/or soft tissue • Appropriate birth control (women of childbearing potential)	n=439	• Dirithromycin 500mg QD x 5d • Erythromycin 250mg q6h x 7d • Dummy tablets were given to protect blinding	7 days (14 day follow up)	**Efficacy: dirithromycin » erythromycin** • There were no statistically significant differences in favorable clinical response rates with any measurements: termination analysis of all patients – 85.0% (d) and 80.8% (e), termination analysis of bacteriologically evaluable patients – 83.0% and 80.2%, and post-therapy analysis (NR). • There were no statistically significant differences in favorable bacteriological response rates with any measurements: termination analysis of all patients – 66.4% (d) and 63.5% (e), termination analysis of bacteriologically evaluable patients – 85.0% and 80.2%, and post-therapy analysis (NR). • S. aureus was isolated from most infections before treatment and was eradicated or presumed eradicated from 78.6% (44/56) of dirithromycin patients and 81.3% (48/59) of erythromycin patients. **Safety: dirithromycin ³ erythromycin** • 167 adverse events were reported by 92 (41.8%) dirithromycin patients, and 182 events were reported by 96 (43.8%) erythromycin patients. • Most common adverse events: headache, abdominal pain, diarrhea, dyspepsia, and nausea. • Nausea was reported more frequently with erythromycin (8.2% vs. 3.6%, p=0.042). • No deaths or serious adverse events related to the study drug were reported. • Four patients in each group discontinued treatment due to adverse events related to the study drug.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Dunne M, et al.[18]	Randomized, double-blind, double-dummy, multicenter	• Blood culture positive for MAC within previous 2 months • HIV infection • Age ≥ 13 years • Expected to survive at least 2 months • ALT and AST <5 ULN • SrCr <3.0mg/dl • Neutrophil count > 500 cells/mm^3	n=181	• Azithromycin 250mg QD (arm terminated) • Azithromycin 600mg QD • Clarithromycin 500mg BID	4 years	**Efficacy: azithromycin » clarithromycin** • An interim analysis at ~2 years demonstrated that patients treated with azithromycin 250mg were less likely to have two consecutive sterile blood cultures at week 12; also, the proportion of patients who had died, although not statistically significant, was higher in the azithromycin 250mg group. These findings met the predefined stopping rule; thus, the azithromycin 250mg arm was closed, and those patients were removed from the study. • Microbiologic efficacy was similar in both groups. 53% of azithromycin patients and 60% of clarithromycin patients had two consecutive negative cultures (sterile) through the last follow-up. Relapse was similar for both treatments. • At week 12, 68.3% (28/41) of azithromycin patients and 91% (29/32) of clarithromycin patients had a satisfactory clinical response (p=0.02). By week 24, 71% (17/24) of azithromycin and 73% (17/23) of clarithromycin patients had improved (p=0.81). • Mortality was similar both by the end of week 24 and at the time of last observation. **Safety:azithromycin = clarithromycin** • Adverse effects, primarily GI, were observed in 63% (53) of azithromycin patients and 66% (56) of clarithromycin patients. • Discontinuations due to adverse events related to the study drug occurred in 10% of azithromycin patients and 6% of clarithromycin patients.
Gonzalez BE, et al.[27]	Retrospective Review	• Children between 1996 and 2002 who received antimicrobials and developed invasive pneumococcal disease within 30 days • Treatment failures was defined as invasive	n=54	• Azithromycin • Beta-lactam antibiotic	7 year retro-spective study	• Eleven (52%) children in the azithromycin group and 11 (33%) in the beta-lactam group met the definition for treatment failures (P = 0.34). • Eight treatment failures while receiving azithromycin were caused by pneumococci with the macrolide-resistant (M) phenotype, 2 with the macrolide-, lincosamide- and streptogramin B-resistant (MLSB) phenotype and 1 by a macrolide-susceptible organism. • In the beta-lactam group 7 had a penicillin-resistant isolate, 3 had an intermediately susceptible isolate and 1 had a susceptible isolate.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
		pneumococcal infection while on antimicrobials or within 3 days of stopping azithromycin or 1 day after stopping a beta-lactam				• Summary: Treatment failures among patients who developed invasive disease within 30 days of receiving an antimicrobial occur as frequently in patients who receive beta-lactam antibiotics as in those who receive azithromycin. Furthermore macrolide resistant organisms are not more likely to be recovered after a macrolide treatment failure than a penicillin-nonsusceptible isolate being recovered after a beta-lactam treatment failure (P = 1.0).
Treadway G, et al.[28]	Tolerability study	• Age < or = 18 years of age • Identified respiratory or skin and soft-tissue infections	n= 2,425	• Azithromycin oral suspension 10mg/kg QD for 3 days • Standard regimens consisting of amoxicillin/ clavulanic acid, cefaclor, cefixime, ceftriaxone, clarithromycin, erythromycin, or penicillin V	Variable, depending on anti-microbial agent used	• The incidence of treatment-related adverse events was significantly lower in patients receiving azithromycin than comparators (7.9 vs. 11.5%, P=0.003), while discontinuation rates were similar (1.0 and 1.1%, respectively). • Significantly fewer gastrointestinal events were recorded for azithromycin than comparators (6.5 vs. 9.9%, P=0.002), and their duration was significantly shorter (mean 2.3 vs. 5.0 days, P=0.0001). • Azithromycin pediatric oral suspension is well tolerated and associated with significantly fewer adverse events than comparators.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
Langley JM, et al.[29]	Large, randomized, controlled trial	• Children 6 months to 16 years of age • Cough illness suspected to be or was culture confirmed as pertussis	n=477	• Azithromycin 10mg/kg on day 1 and 5mg/kg on days 2-5 as a single dose • Erythromycin estolate 40mg/kg/day in 3 divided doses for 10 days	5 days course vs. 10 day course	• At end of therapy, bacterial eradication was demonstrated in all 53 patients in the azithromycin group and all 53 patients in the erythromycin group with follow-up cultures available (eradication 100%; 95% confidence interval [CI]: 93.3-100). • No bacterial recurrence was demonstrated in children with 1week posttreatment nasopharyngeal cultures available (51 and 53 participants in the azithromycin and erythromycin arms, respectively [0%, 95% CI: 0-7.0; and 0%, 95% CI: 0-6.7]). • Gastrointestinal adverse events were reported less frequently in azithromycin (18.8%; 45 of 239) than in erythromycin estolate (41.2%; 98 of 238) recipients (90% CI on difference: -29.0% to -15.7%) as a result of less nausea (2.9% vs 8.4%; 95% CI: -8.9% to -2.0%), less vomiting (5.0% vs 13.0%; 95% CI: -4.9% to -1.4%), and less diarrhea (7.1% vs 11.8%; 95% CI: -9.0% to -0.3%). • Children who were randomized to azithromycin were much more likely to have complied with antimicrobial therapy over the treatment period. In the azithromycin group, 90% of children took 100% of prescribed doses, whereas only 55% of children in the erythromycin group took 100% of prescribed doses. • Summary: Azithromycin is as effective as erythromycin estolate for the treatment of pertussis in children. Gastrointestinal adverse events were much more common with erythromycin treatment than azithromycin. Compliance with therapy was markedly better with azithromycin than with erythromycin in this study.
Contopoulos-Ioannidis DG, et al.[30]	Meta-analysis of randomized controlled trials of azithromycin compared to	• Patients with lower respirtory tract infections, including acute bronchitis, acute exacerbations of	n=36 studies and 4,378 patients	• Azithromycin • Other antibiotics for lower respiratory tract infections	Variable	• For acute bronchitis and exacerbations of chronic bronchitis, azithromycin did not offer any statistically significant reduction in clinical failures [random effects odds ratios 0.84, 95% confidence interval (CI) 0.54-1.31 and 0.64, 95% CI 0.31-1.32, respectively] and absolute risk differences were small.

Reference	Study Design	Entry Criteria	N	Treatment Regimen	Duration of Study	Results
	other antibiotics for lower respiratory tract infections	chronic bronchitis, and community-acquired pneumonia				• For community-acquired pneumonia, azithromycin significantly reduced clinical failures by about one-third (random effects odds ratio 0.63, 95% CI 0.41-0.95). • The absolute incremental benefit was approximately one clinical failure prevented per 50 treated patients with community-acquired pneumonia. • Azithromycin was discontinued because of adverse events in only 23 of 3487 patients (0.7%). • Summary: Compared with antibiotics with traditional pharmacokinetics that require more prolonged courses, azithromycin offers no significant advantage for bronchitis, but may be more effective in community-acquired pneumonia.

Key

ALT = Alanine aminotransferase	d = day(s)	MAC = *Mycobacterium avium* complex	QD = Once daily
AST = Aspartate aminotransferase	GI = gastrointestinal	NR = Not reported	SrCr = Serum creatinine
BID = twice daily	HIV = human immunodeficiency virus	Q = Every	ULN = Upper limit of normal

Additional Evidence

Dose Simplification: The drugs in this class are for serious bacterial infections. Most frequently, the IV therapies are given during hospitalization or via nursing care within extended care facilities. Most of the anti-infectives in this class and other alternatives are once or twice daily drugs.

In a comparative study by Sopena N, et al., the efficacy and tolerability of azithromycin versus clarithromycin in community-acquired pneumonia was evaluated.[31] Seventy patients were randomized to azithromycin 500mg QD for three days or clarithromycin 250mg BID for ten-fourteen days. No differences in response rates were detected in the two treatment groups, even though azithromycin compliance was superior to clarithromycin (no cases of azithromycin non-compliance versus 15 cases of clarithromycin non-compliance). There were no treatment failures in either of the treatment groups. The frequency of adverse events was similar in the two groups.

Although some of the studies presented in the evidence table of this review showed that azithromycin and clarithromycin are better tolerated and result in improved compliance (mainly with azithromycin), published studies have not measured a direct correlation between these factors and any subsequent impact on the outcome of the infection.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical studies that have evaluated the effect of changing from one macrolide antibiotic to another during the same course of therapy.

Impact on Physician Visits: Due to the nature of use of the drugs in this class, and to their indications, no published studies have evaluated the impact of use of these drugs on physician visits. A search of Medline and Ovid did not reveal data pertinent to this topic.

IX. Conclusions

Although azithromycin and clarithromycin may offer more indications for pediatric use and certain pneumonias, azithromycin, clarithromycin, dirithromycin, and erythromycin all demonstrate similar efficacy when evaluated for general use. Indications for use, duration of therapy, drug interactions, and drug safety should be taken into consideration when selecting an agent. However, the clinical evidence does not support use of one agent as a result of any of these factors, in general use.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand single entity macrolide is recommemded for preferred status.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Macrolide Antibiotics
Combination Agents
AHFS 081212
January 26, 2005

I. Overview [1, 6]

Erythromycin ethylsuccinate and sulfisoxazole is a combination available as a suspension for the treatment of acute otitis media caused by susceptible strains of Haemophilus influenzae. Erythromycin-sulfisoxazole may also be used to treat other infections of the upper respiratory tract. This combination provides adequate coverage against many strains of S. pneumoniae, S. pyogenes, H. influenzae, and M. catarrhalis and is especially useful in patients allergic to penicillins and cephalosporins. Erythromycin-sulfisoxazole was granted FDA approval for the treatment of acute otitis media in November, 1979. [1, 6]

This review encompasses all dosage forms and strengths.

Table 1. Combination Macrolide Antibiotics in this Review[6]

Generic Name	Formulation	Example Brand Name
Erythromycin and Sulfisoxazole	Granules for Oral Suspension: Erythromycin ethylsuccinate (equivalent to 200mg erythromycin activity) and sulfisoxazole acetyl (equivalent to 600mg sulfisoxazole) per 5ml when reconstituted	Pediazole

Table 2. Comparison of Bacterial Coverage of Erythromycin and Sulfisoxazole[1, 6]

Drug	Spectrum
Erythromycin and Sulfisoxazole	Erythromycin ethylsuccinate is a macrolide antibiotic and inhibits bacterial protein synthesis by reversible binding to the 50 S ribosomal subunits of susceptible organisms. Sulfisoxazole interferes with microbial folic acid synthesis and inhibits bacterial growth. Sulfisoxazole inhibits bacterial dihydropteroate synthase and interferes with the conversion of p-aminobenzoic acid (PABA) into folic acid, an essential component of bacterial development. Sulfisoxazole is bacteriostatic. Although erythromycin and sulfisoxazole is indicated only for the treatment of acute otitis media caused by susceptible strains of Haemophilus influenzae, both antimicrobials have some activity against S. pneumoniae. S. pneumoniae is another common pathogen in patients with acute otitis media. The resistance of S. pneumoniae to erythromycin and sulfisoxazole is increasing therefore the usefulness of this combination for the treatment of infections caused by S. pneumoniae may be limited.

II. Indications of the Combination Macrolide Antibiotics

Erythromycin and sulfisoxazole is approved for use in children for the treatment of Acute otitis media caused by susceptible strains of Haemophilus influenzae. [1, 6]

III. Pharmacokinetic Parameters

Erythromycin-sulfisoxazole suspension forms a stable, tasteless suspension in water. Erythromycin ethylsuccinate is well absorbed from the gastrointestinal tract. Erythromycin is primarily bound to plasma proteins. It diffuses readily into most body fluids except the brain and cerebrospinal fluid. The ratio of the concentration of erythromycin achieved in middle ear exudates in otitis media to the concentration achieved in serum is 0.3-0.7. Erythromycin crosses the placental barrier and is excreted in human milk. The drug is concentrated in the liver and excreted primarily in the bile; only 2-5% of a dose is excreted in the urine. The serum half-life of erythromycin is about 1.4 - 2 hours. The half-life may be prolonged up to about five hours in anuric patients.

Sulfisoxazole is rapidly and completely absorbed following oral administration. Sulfonamides are present in the blood as free (considered to be the therapeutically active form), conjugated (acetylated and possibly other forms), and protein-bound forms. About 85% of a dose of sulfisoxazole is bound to plasma proteins, which is primarily albumin. Time to peak plasma concentrations following a single 2 g dose of sulfisoxazole to healthy adult volunteers ranges from 1 to 4 hours (mean: 2.5 hours). Maximum plasma concentrations after a single 2 g dose range from 127-211 mcg/ml (mean: 169mcg/ml). Sulfisoxazole is distributed only in extracellular body fluids. It readily crosses the placental barrier and is excreted in human milk. Sulfisoxazole and its acetylated metabolites are excreted primarily by the kidneys. The elimination half-life of sulfisoxazole is about 4.6-7.8 hours. [1, 6]

Table 3. Pharmacokinetic Parameters of the Combination Macrolide [1, 6]

Drug	Mechanism of Action	Bioavailability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Erythromycin/ sulfisoxazole	Erythromycin inhibits bacterial protein synthesis by reversible binding to the 50 S ribosomal subunits. Sulfisoxazole inhibits bacterial growth via interference with microbial folic acid synthesis.	<35%	73-81%	hepatic	none	biliary	Erythromycin 1.5-2 hours in normal renal function

IV. Drug Interactions

Table 4 lists the most significant drug drug-interactions (Level 1 and 2) for the drugs indexed by Drug Interactions Facts.[9]

Table 4. Drug Interactions of the Combination Macrolide Antibiotics[7]

Drug	Significance	Interaction	Mechanism
Erythromycin (Erythromycin/ Sulfisoxazole)	Level 1	Warfarin Sodium	The total body clearance of WARFARIN is reduced.
	Level 1	Carbamazepine	Inhibition of CARBAMAZEPINE (CBZ) hepatic metabolism (CYP3A4), leading to decreased CBZ clearance
	Level 1	Cisapride†	Certain MACROLIDE ANTIBIOTICS may inhibit the hepatic metabolism (CYP3A4) of CISAPRIDE.
	Level 1	Digoxin	Certain MACROLIDE ANTIBIOTICS may inhibit renal tubular P-glycoprotein excretion of DIGOXIN.2 Genetic variation in this effect is suspected.3
	Level 1	Dihydroergotamine, Ergotamine	Although the mechanism is uncertain, it is hypothesized that MACROLIDE ANTIBIOTICS interfere with the hepatic metabolism of ERGOTAMINE.1
	Level 1	Atorvastatin, Lovastatin, Simvastatin, Cerivastatin†	Inhibition of metabolism (CYP3A4) is suspected.
	Level 1	Pimozide	MACROLIDE ANTIBIOTICS may inhibit the hepatic metabolism (CYP3A4) of PIMOZIDE.
	Level 1	Gatifloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin	Unknown.
	Level 1	Vinblastine	Possible inhibition of VINBLASTINE metabolism by ERYTHROMYCIN
	Level 2	Alprazolam, Diazepam, Midazolam HCl, Triazolam	Decreased metabolism of certain BENZODIAZEPINES
	Level 2	Buspirone	Possibly because of inhibition by a MACROLIDE ANTIBIOTIC of the CYP3A4 isozyme responsible for first-pass metabolism of BUSPIRONE.
	Level 2	Cilostazol	Certain MACROLIDE ANTIBIOTICS may inhibit the metabolism (CYP3A4) of CILOSTAZOL.
	Level 2	Methylprednisolone	Although this interaction results in an increase in plasma concentrations of METHYLPREDNISOLONE, it is unclear if this alone is responsible for the marked increase in METHYLPREDNISOLONE's effect.
	Level 2	Cyclosporine	MACROLIDE ANTIBIOTICS may interfere with CSA metabolism and may increase rate and extent of absorption or reduce volume of distribution.1-8
	Level 2	Grapefruit Juice and Food	FOOD may decrease GI absorption of nonenteric-coated ERYTHROMYCIN base tablets and stearate. GRAPEFRUIT may inhibit the metabolism (CYP3A4) in the small intestine.
	Level 2	Repaglinide	Certain MACROLIDE ANTIBIOTICS may inhibit first-pass metabolism (CYP3A4) of REPAGLINIDE.
	Level 2	Rifabutin, Rifampin, Rifapentine	RIFAMYCIN metabolism may be inhibited, while MACROLIDE ANTIBIOTIC metabolism may be increased.
	Level 2	Tacrolimus	Inhibition of TACROLIMUS hepatic metabolism (CYP3A4).
	Level 2	Aminophylline, Oxtriphylline, Theophylline	Certain MACROLIDES inhibit the metabolism of THEOPHYLLINE; THEOPHYLLINE reduces the bioavailability and increases renal clearance of oral ERYTHROMYCIN.
	Level 2	Bromocriptine	Because ERYTHROMYCIN is known to inhibit hepatic metabolism of other drugs, increased bioavailability because of decreased hepatic first-pass metabolism may be involved.
Sulfisoxazole (erythromycin and sulfisoxazole)	Level 1	Methotrexate	SULFONAMIDES displace MTX from protein binding sites and decrease renal clearance of MTX.2, 4 MTX may induce folate deficiency, which develops into acute megaloblastic anemia upon administration of TMP-SMZ.

	Level 2	Sulfonylureas	SULFONAMIDES may impair hepatic metabolism of SULFONYLUREAS or alter plasma protein binding.

Table 5. Additional Drug-Drug Interactions for Macrolide Antibiotics[7]

Macrolide Antibiotic Drug Interactions			
Precipitant Drug	Object Drug*		Description
Antacids	Macrolides Azithromycin Dirithromycin Erythromycin	↔	Aluminum- and magnesium-containing antacids reduce peak serum levels but not the extent of azithromycin absorption. When given immediately following antacids, dirithromycin absorption is slightly enhanced. When given immediately prior to antacids, the elimination rate constant of erythromycin may be slightly decreased.
Fluconazole	Macrolides Clarithromycin	↑	Coadministration led to increases in mean steady-state trough levels (33%) and AUC (18%) of clarithromycin.
H_2 antagonists	Macrolides Dirithromycin	↑	When given immediately after H_2 antagonists, dirithromycin absorption is slightly enhanced.
Macrolides Clarithromycin	Ranitidine bismuth citrate	↔	Coadministration resulted in increased plasma ranitidine levels (57%), increased plasma bismuth trough concentrations (48%), and increased 14-OH clarithromycin plasma levels (31%). These effects do not appear to be clinically important.
Ranitidine bismuth citrate	Macrolides Clarithromycin		
Pimozide	Macrolides Azithromycin Clarithromycin Dirithromycin Erythromycin	↑	Coadministration is contraindicated. Two sudden deaths have occurred when clarithromycin was added to ongoing pimozide therapy.
Rifamycins Rifabutin Rifampin	Macrolides Clarithromycin Erythromycin Troleandomycin	↓	The antimicrobial effects of the macrolide antibiotic may be decreased while the frequency of GI adverse effects may be increased.
Macrolides Erythromycin	Alfentanil	↑	Alfentanil clearance may be decreased and the elimination half-life increased.
Macrolides Clarithromycin Erythromycin	Anticoagulants, oral	↑	Anticoagulant effects may be potentiated. Until more data are available, it is prudent to monitor anticoagulant function in patients receiving anticoagulants and any macrolide antibiotic.
Macrolides Clarithromycin Erythromycin Troleandomycin	Benzodiazepines Alprazolam Diazepam Midazolam Triazolam	↑	The plasma levels of certain benzodiazepines may be elevated, increasing and prolonging the CNS depressant effects. Azithromycin and dirithromycin would not be expected to interact.
Macrolides Erythromycin	Bromocriptine	↑	Bromocriptine serum levels may be elevated, resulting in an increase in the pharmacologic and adverse effects.
Macrolides Clarithromycin Erythromycin Troleandomycin	Buspirone	↑	Plasma buspirone concentrations may be elevated, increasing the pharmacologic and adverse effects. Azithromycin and dirithromycin would not be expected to interact.
Macrolides Clarithromycin Erythromycin Troleandomycin	Carbamazepine	↑	Increased concentrations of carbamazepine may occur. Azithromycin and dirithromycin would not be expected to interact.
Macrolides Clarithromycin Erythromycin Troleandomycin	Cisapride	↑	Coadministration of these drugs is contraindicated. Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT interval prolongation may occur. Azithromycin and dirithromycin would not be expected to interact with cisapride.
Macrolides Azithromycin Clarithromycin Erythromycin Troleandomycin	Cyclosporine	↑	Elevated cyclosporine concentrations with increased risk of toxicity (nephrotoxicity, neurotoxicity) may occur. Azithromycin and dirithromycin would not be expected to interact. However, a single case report implied that azithromycin may interact with cyclosporine.

Macrolides Clarithromycin Erythromycin	Digoxin	↑	Serum digoxin concentrations may be elevated because of the effect of the antibiotic on gut flora that metabolizes digoxin in ≈10% of patients. Carefully monitor patients receiving digoxin and any macrolide antibiotic.
Macrolides Clarithromycin Erythromycin	Disopyramide	↑	Disopyramide plasma levels may be increased. Arrhythmias and Increased QT_c intervals have occurred.
Macrolides Clarithromycin Erythromycin Troleandomycin	Ergot alkaloids	↑	Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has occurred. Carefully monitor patients receiving ergot alkaloids and any macrolide antibiotic.
Macrolides Erythromycin	Felodipine	↑	Felodipine plasma levels may be elevated, increasing pharmacologic and adverse effects.
Macrolides Erythromycin	Fluoroquinolones Grepafloxacin Sparfloxacin	↑	Sparfloxacin is contraindicated with erythromycin while grepafloxacin is contraindicated unless appropriate cardiac monitoring can be ensured (e.g., hospitalized patients). Risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased with coadministration.
Macrolides Azithromycin Clarithromycin Erythromycin	HMG-CoA reductase inhibitors	↑	The risk of severe myopathy or rhabdomyolysis may be increased.
Macrolides Erythromycin	Lincosamides	↓	Under some conditions, coadministration may be antagonistic.
Macrolides Erythromycin Troleandomycin	Methylprednisolone	↑	The clearance of methylprednisolone is greatly reduced. This has been used as a therapeutic advantage to reduce the dose.
Macrolides Clarithromycin	Omeprazole	↑	Coadministration may result in increased plasma levels of omeprazole, clarithromycin, and 14-OH clarithromycin.
Omeprazole	Macrolides Clarithromycin		
Macrolides Troleandomycin	Oral contraceptives	↑	Concurrent use may result in increased risk of intrahepatic cholestasis caused by decreased metabolism and accumulation of the contraceptive.
Macrolides Erythromycin	Penicillins	↔	Both antagonism and synergism have occurred with coadministration.
Macrolides Clarithromycin Erythromycin Troleandomycin	Tacrolimus	↑	Concurrent use may be associated with elevated serum tacrolimus levels, increasing the risk of side effects (e.g., nephrotoxicity). Azithromycin and dirithromycin would not be expected to interact.
Macrolides Clarithromycin Erythromycin Troleandomycin	Theophylline	↑	Concurrent use may be associated with increased serum theophylline levels. Azithromycin and dirithromycin would not be expected to interact. Monitor serum theophylline levels in patients receiving theophylline and any macrolide antibiotic. In addition, plasma erythromycin levels may be decreased.
Theophylline	Macrolides Erythromycin	↓	
Macrolides Erythromycin	Vinblastine	↑	Risk of vinblastine toxicity (e.g., constipation, myalgia, neutropenia) may be increased.
Macrolides Clarithromycin	Zidovudine	↔	Peak serum zidovudine concentrations may be increased or decreased.

↑ = Object drug increased. ↓ = Object drug decreased. ↔ = Undetermined clinical effect.

V. Adverse Events of the Combination Macrolide Antibiotics

Table 6. Common Adverse Events (%) Reported for the Erythromycin-Sulfisoxazole[1, 6, 19, 20]

	Erythromycin	Sulfisoxazole
Adverse Events (%) [1-8] >1% occurrence		
Body as a Whole		
Asthenia	1.4-1.9	
Elevated CPK	0.7-0.9	
Pain (non-specific)	1.6-3.0	√
Central Nervous System		
Dizziness/vertigo	2.0-2.3	√
Headache	7.6-8.2	√
Insomnia	0.7-1.1	
Dermatologic		
Pruritus/urticaria	0.6-1.0	√
Rash	1.4-2.6	√
Gastrointestinal		
Abdominal pain	6.2-7.5	
Abnormal taste	--	
Anorexia	√	√
Diarrhea/loose stools	7.3-9.4	√
Dyspepsia	2.1-2.7	
Flatulence	1.5-1.6	
GI disorder	0.2-1.4	
Nausea	7.5-8.7	√
Vomiting	1.3-2.8	√
Hematologic		
Decreased hematocrit	--	
Decreased hemoglobin	--	
Decreased lymphocytes	--	
Elevated eosinophils	0.6-0.9	
Elevated leukocytes	0.9-1.2	
Elevated seg neutrophils	1.3-2.3	
Increased platelet count	1.4-4.8	
Hepatic		
Elevated ALT	--	
Elevated AST	--	
Elevated GGT	--	
Elevated LDH	--	
Elevated total bilirubin	--	
Renal		
Elevated BUN	--	
Elevated SrCr	--	

	Erythromycin	Sulfisoxazole
Respiratory		
Dyspnea	1.2-1.6	
Increased cough	0.5-2.6	
Other		*
Sudden cardiac death[19,20]	√	
Decreased bicarbonate	2.0	
Elevated potassium	--	
Vaginitis	0.6	

* Sulfisoxazole can also cause fulminant hepatic necrosis; agranulocytosis; aplastic anemia; thrombocytopenia; pancytopenia; and other blood dyscrasias.

√ Adverse event reported, specific percentages not available.

VI. Dosage and Administration for the Combination Macrolide Antibiotics[1]

Table 7. Dosing for the Combination Macrolide Antibiotics[1, 6]

Drug	Availability	Dose/Frequency/Duration
Erythromycin/ Sulfisoxazole	Erythromycin Ethylsuccinate, 200mg/5ml Sulfisoxazole Acetyl, 600mg/5ml	Children and infants >= 2 months: The recommended dose is 40-50mg/kg/day PO of the erythromycin component given in divided doses every 6-8 hours for 10 days. Do not exceed 2g erythromycin or 6g sulfisoxazole per day. Infants < 2 months: Erythromycin-sulfisoxazole is contraindicated in this age group.

Erythromycin/Sulfisoxazole Dosage Based on Weight

Weight		Dose (every 6 hours)
kg	lb	
< 8	< 18	Adjust dosage by body weight
8	18	2.5ml
16	35	5ml
24	53	7.5ml
> 45	> 100	10ml

Special Dosing Considerations

Table 8. Special Dosing considerations for the Combination Macrolide Antibiotics[1, 6]

Drug	Renal Dosing?	Hepatic dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed/Stability
Erythromycin/ Sulfisoxazole	No guidelines ; use with caution	No guidelines; use with caution	Yes, refer to dosing guidelines in table 7.	C	After mixing, store in the refrigerator between 2 and 8 degrees C (36 and 46 degrees F). Do not freeze. Throw away any unused medicine after 14 days.

VII. Comparative Efficacy

Table 9. Additional Outcomes Evidence for the Combination Macrolide Antibiotics

Study	Sample	Treatment/Duration	Results
Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion in children.[21]	-	Duration: Prevalence of middle-ear effusion 2 and 4 weeks after entry into study.	To determine whether children with otitis media treated with either erythromycin-sulfisoxazole or cefaclor would have greater short term efficacy than found for amoxicillin • Final analysis showed no significant difference between-groups in outcome measures. • Conclude that when antimicrobial treatment for otitis media with effusion is deemed advisable, neither erythromycin-sulfisoxazole nor cefaclor should replace amoxicillin as first line treatment.
Otitis media-related antibiotic prescribing patterns and outcomes in a pediatric Medicaid population.[22]	n=12,381	2years Prospective analysis of meropenem patients and retrospective analysis of imipenem/cilastatin patients	Analysis to document the antibiotic used to treat new episodes of acute otitis media, factors influencing antibiotic selection, and the short term outcomes. • The average rate of prescribing a second course of antibiotics within 24 days after initial antibiotic treatment of a new acute otitis media episode was 11.6% when group A antibiotics (amoxicillin, trimethoprim plus sulfamethoxazole, or erythromycin plus sulfisoxazole) were prescribed, and 13.2% when group B antibiotics (cefaclor, amoxicillin plus clavulanate, or cefixime) were prescribed. • The average adverse drug reaction rate was 5.9% when group A antibiotics were prescribed, compared with 6.1% when group B antibiotics were prescribed. • The findings of this study document a preference for amoxicillin as the initial antibiotic for a new episode of acute otitis media.
An open randomized trial, Pediazole versus cefaclor in the treatment of acute otitis media in children[23]	n=103	Daily dose of cefaclor 40-50mg/kg and erythromycin 50 mg/kg + Sulf. 150 mg/kg (ES) given in three divided doses per day for ten days	Clinical results: • Failures before or at completion of the course, 5/52 in the ES group versus 13/51 in the cefaclor group, for the treatment of children with acute otitis media.
Acute otitis media in children: a randomized and open clinical trial of the efficacy of 2 major antibiotics (erythromycin ethylsuccinate/acetyl sulfafurazole vs amoxicillin/clavulanic acid.[24]	n=111	Treatment for 10 days with erythromycin 50 mg/kg + Sulf. 150 mg/kg (ES) in 3 divided doses) or amoxicillin + clavulanic acid (40 mg/kg/day in 3 or 4 divided doses)	In comparing the efficacy and safety: • There was no statistically significant difference between the two treatment groups for efficacy. • Overall safety was good for both groups. • Conclusion: Erythromycin sulfisoxazole combination fits in with current epidemiological profile of Acute Otitis Media and represents a therapy of choice in this indication.

Additional Evi dence

Dose Simplification: A literature search of Medline and Ovid did not reveal studies that have looked at adherence with erythromycin/sulfisoxazole compared to other antibiotics, and any correlation found with improved compliance with lower dosing frequencies. Multiple antibiotics are available for children with otitis media, some are available in oral liquid formulations with less frequent dosing regimens. No studies have evaluated whether improved compliance has any effect on the outcome of otitis media.

Stable Therapy: Antibiotic regimens should be changed due to lack of improvement of the disease, or due to resistant organisms. Otherwise, antibiotics should not be routinely switched. No further data was found in a literature search of Medline of Ovid pertinent to the drugs in this class and changing treatments during a course of therapy.

Impact on Physician Visits: A search of Medline and Ovid did not reveal data pertinent to medical or physician resource utilization.

VIII. Conclusion

While the current American Academy of Pediatrics treatment guidelines for otitis media suggest some physicians may elect observation with symptomatic treatment instead of antibiotic therapy, the aminopenicillins (amoxicillin) remain the first-line treatment for **most** children with otitis media.[32] Amoxicillin/clavulanate is recommended for more severe illness and cefdinir, cefpodoxime, and cefuroxime are recommended for children allergic to amoxicillin. Alternative recommended therapies include azithromycin, clarithromycin, erythromycin-sulfisoxazole, and sulfamethoxazole-trimethoprim. Clinical data presented suggests erythromycin/sulfisoxazole and other antibiotics for otitis media are comparable in efficacy and safety. Additionally, generic options are available for many of the recommended first-line agents.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in that class and offer no significant clinical advantage over other alternatives in general use.

IX. Recommendation

No brand combination macrolide antibiotic is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Quinolones
AHFS 081218
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I. Overview

The fluoroquinolones are synthetic, broad-spectrum antibacterial agents that inhibit DNA gyrase and topoisomerase IV.[1-4] DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme that plays a key role in the partitioning of the chromosomal DNA during bacterial cell division.

The broad category of fluoroquinolones refers to antibacterials characterized by the addition of a fluorine atom to the quinolone structure of drugs such as nalidixic acid and cinoxin. These two agents are classified as first generation quinolones. The second generation quinolones, ciprofloxacin, lomefloxacin, norfloxacin, and ofloxacin, came to market in the mid 1980s. Compared to non-fluorinated quinolones, these agents have improved pharmacokinetics and increased gram-negative and systemic activity. Clinical uses include uncomplicated and complicated urinary tract infections (UTIs) and pyelonephritis, sexually transmitted diseases (STDs), prostatitis, and skin and soft tissue infections. Ciprofloxacin is the most potent fluoroquinolone against *Pseudomonas aeruginosa*.[1] However, resistance to ciprofloxacin has developed in strains of *P. aeruginosa* and *Serratia marcescens*. Ciprofloxacin also has good penetration into bone that makes it a useful alternative to parenteral antibiotics for the treatment of osteomyelitis caused by susceptible organisms.[2] Additionally, ciprofloxacin is the only fluoroquinolone approved for the treatment of anthrax infection. Ofloxacin is the most active second generation quinolone against *Chlamydia trachomatis*, and it exhibits the greatest activity of the group against *Staphylococcus aureus*. Lomefloxacin has the longest half-life of the group and can, therefore, be administered once daily.

The third generation quinolones include gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and sparfloxacin. Levofloxacin is the levo- isomer and more active component of the ofloxacin racemic mixture. Third generation fluoroquinolones have extended activity against gram-positive pathogens, particularly penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae*, and atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[1-3] Third generation agents also have broad gram-negative coverage but are less active than ciprofloxacin against *Pseudomonas* species. The long half-lives of gatifloxacin, gemifloxacin, and moxifloxacin allow once daily dosing. Clinical uses include community-acquired pneumonia, acute sinusitis, and acute exacerbations of chronic bronchitis. Gatifloxacin is also approved for treating UTIs and gonorrhea. Levofloxacin, also indicated to treat UTIs and skin and skin structure infections, recently received FDA approval for the treatment of chronic bacterial prostatitis. This review encompasses all dosage forms and strengths.

Table 1. Quinolones in this Review

Generic Name	Formulation	Example Brand Name (s)
Ciprofloxacin	Oral, Injection	*Cipro, Cipro XR, Cipro Cystitis Pack
Gatifloxacin	Oral, Injection	Tequin
Gemifloxacin	Oral	†Factive
Levofloxacin	Oral, Injection	Levaquin
Lomefloxacin	Oral	Maxaquin
Moxifloxacin	Oral, Injection	Avelox, Avelox ABC Pack
Norfloxacin	Oral	Noroxin
Nalidixic Acid	Oral	NegGram
Ofloxacin	Oral, Injection	*Floxin
Sparfloxacin	Oral	Zagam

*Generic Available. † Factive was FDA approved September 7, 2004. Per Alabama Medicaid P&T policy, gemifloxacin is eligible for review after it has been commercially available for at least 6 months. Gemifloxacin will be reviewed at a future time. Additionally, Trovan (trovafloxacin/alatrofloxacin) oral and intravenous, per the manufacturer, was discontinued as of February 2003.

II. Evidence Based Medicine and Current Treatment Guidelines

Like several of the anti-infective classes, the quinolones are important antibiotics for many different infections. The most common treatment guidelines that utilize the quinolones include those for sexually transmitted diseases and community-acquired pneumonia.

Sexually Transmitted Diseases

The Centers for Disease Control and Prevention (CDC) clinical guidelines for sexually transmitted diseases include use of quinolones for the following infections: nongonococcal urethritis (alternative therapy with ofloxacin or levofloxacin), chlamydial infections in adolescents and adults (alternative therapy with ofloxacin or levofloxacin), uncomplicated gonococcal infections of the cervix, urethra, and rectum (ciprofloxacin, ofloxacin, or levofloxacin), uncomplicated gonococcal infections of the pharynx (ciprofloxacin), and disseminated gonococcal ingestion (alternative therapy with ciprofloxacin, ofloxacin, or levofloxacin).[5] However, quinolones are no longer recommended for the treatment of gonorrhea, due to resistance, in the state of Hawaii or in infections acquired in Asia or the Pacific area. Increased resistance has been documented in the United States in California, and resistance is expected to spread.

Community-Acquired Pneumonia

Quinolones are included in the treatment guidelines for community-acquired pneumonia as alternative first-line therapies, and are first-line in combination with cefepime, an aminoglycoside, or azithromycin for severe pneumonias complicated by structural disease of the lung.[6]

III. Comparative Indications of the Quinolones

Table 2 lists the FDA-approved indications for the quinolones.

Table 2. FDA-Approved Indications for the Quinolones[1-4]

Indications	Cipro+[12] Cipro®	Gati+ Tequin®	Levo+ Levaquin®	Lome+ Maxaquin®	Moxi+ Avelox®	Nor+ Noroxin®	Nalidixic Acid NegGram®	O+ Floxin®	Spar+ Zagam®
Uncomplicated UTI's[2] (cystitis)	X[3]	X	X	X		X	X	X[4]	
Complicated UTI's[2]	X[5]	X	X	X		X		X	
Acute pyelonephritis	X[6]	X[4]	X[4]						
Prostatitis						X		X[4]	
Chronic Bacterial Prostatitis	X		X						
Nongonococcal urethritis and cervicitis								X	
Mixed infections of the urethra and cervix								X	
Uncomplicated cervical and urethral gonorrhea	X	X				X		X[7]	
Acute PID								X	
Acute, uncomplicated rectal infections in women		X							
Complicated Intra-Abdominal Infections	X								
Inhalation Anthrax	X[5]								
Acute Exacerbation of Chronic Bronchitis	X	X	X	X	X			X	X
Acute Sinusitis	X	X	X		X				
Nosocomial pneumonia			X						
Community acquired pneumonia	X[5]	X	X*		X			X	X
Infectious diarrhea	X								
Typhoid Fever (Enteric Fever)	X								
Skin and Skin Structure Infections	X	X[9]	X[9, 10]		X[9, 10]			X[9]	
Bone and Joint Infections	X								
Preoperatively for prevention of infection[11]				X					

+ floxacin

1 Enoxacin (Penetrex) was discontinued in August 2001and no generics are available.

2 UTI = urinary tract infection

3 Acute, in females

4 Due to *E. coli*

5 In patients =1 year of age and adults, precautions exist for pediatric use.

6 In patients 1-17 years of age only, precautions exist for pediatric use.

7 Including post-surgical infections

8 PID= pelvic inflammatory disease

9 Uncomplicated

10 Complicated skin and skin structure infections.

11 Infections in the following situations: transrectal prostate biopsy and transurethral surgical procedures.

*In September of 2004, levofloxacin received a new indication for community-acquired pneumonia due to strains of multi-drug resistant strains of *S. pneuminiae*.

12 Cipro XR only indicated for complicated and uncomplicated UTI and acute uncomplicated pyelonephritis.

IV. Pharmacokinetic Parameters

Table 3 lists the pharmacokinetic parameters of the quinolone antibiotics.

Table 3. Pharmacokinetic Parameters of the Quinolones[4]

Quinolone	Bioavailability (%)	Max urine concentration (mcg/mL) (dose)	Mean peak plasma concentration (mcg/mL) (dose)	Area under curve (AUC) (mcg ·hr/mL) (dose)	Protein binding (%)	t1/2 (hr)	Urine recovery unchanged (%)
Ciprofloxacin Oral	≈70-80	> 200 (250mg)	1.2 (250mg) 2.4 (500mg) 4.3 (750mg) 5.4 (1000mg)	4.8 (250mg) 11.6 (500mg) 20.2 (750mg) 30.8 (1000mg)	20-40	≈4	≈40-50
IV		> 200 (200mg) >400 (400mg)	4.4 (400mg)	4.8 (200mg) 11.6 (400mg)		≈5-6	≈50-70
Enoxacin	≈90	nd[1]	0.93 (200mg) 2 (400mg)		≈40	3-6	> 40
Gatifloxacin[2] Oral	≈96		≈2 (200mg single dose) ≈3.8 (400mg single dose) ≈4.2 (400mg multiple dose)	≈14.2 (200mg single dose) ≈33 (400mg single dose) ≈34.4 (400mg multiple dose)	≈20	≈7.8 (400mg single dose) ≈7.1 (400mg multiple dose)	≈73.8 (200mg single dose) ≈72.4 (400mg single dose) ≈80.2 (400mg multiple dose)
IV			≈2.2 (200mg single dose) ≈2.4 (200mg multiple dose) ≈5.5 (400mg single dose) ≈4.6 (400mg multiple dose)	≈15.9 (200mg single dose) ≈16.8 (200mg multiple dose) ≈35.1 (400mg single dose) ≈35.4 (400mg multiple dose)		≈11.1 (200mg single dose) ≈12.3 (200mg multiple dose) ≈7.4 (400mg single dose) ≈13.9 (400mg multiple dose)	≈71.7 (200mg single dose) ≈72.4 (200mg multiple dose) ≈62.3 (400mg single dose) ≈83.5 (400mg multiple dose)
Levofloxacin	≈99		≈2.8-11.5 (single dose oral or IV) ≈5.7-12.1 (multiple dose oral or IV)	≈27.2-110 (single dose oral or IV) ≈47.5-108 (multiple dose oral or IV)	≈24-38	≈6.3-7.5 (single dose oral or IV) ≈7-8.8 (multiple dose oral or IV)	≈87 (oral)
Lomefloxacin	≈95-98	> 300 (400mg)	0.8 (100mg) 1.4 (200mg) 3.2 (400mg)	5.6 (100mg) 10.9 (200mg) 26.1 (400mg)	≈10	≈8	≈65
Moxifloxacin	≈90		4.5 (400mg)	≈48 (400mg)	≈50	≈12	≈20
Norfloxacin	30-40	= 200 (400mg)	0.8 (200mg) 1.5 (400mg) 2.4 (800mg)		10-15	3-4	26-32
Ofloxacin Oral	≈98	≈220 (200mg)	1.5 (200mg) 2.4 (300mg) 2.9 (400mg) 4.6 (400mg steady-state)	14.1 (200mg) 21.2 (300mg) 31.4 (400mg) 61 (400mg steady-state)	≈32	≈9	65-80

IV		nd[1]	2.7 (200mg) 4 (400mg)	43.5 (400mg)	≈32	5-10	≈65
Sparfloxacin	92	> 12 (400mg)[3]	≈1.3 (400mg)	≈34 (400mg)	≈45	≈20	≈10

[1] nd = no data.

[2] Single dose: AUC (0-∞); Multiple dose: AUC(0-24).

[3] Following a 400mg loading dose of sparfloxacin, the mean urine concentration 4 hours postdose was in excess of 12mcg/mL.

V. Drug Interactions

Significant drug interactions can effect the treatment course of the quinolones, both drug-drug and drug-food interactions. Table 4 describes the most significant (Level 1 and 2) drug interactions for the quinolones.

Drug / Lab test interactions:
Sparfloxacin therapy may produce false-negative culture results for *Mycobacterium tuberculosis* by suppression of mycobacterial growth.[2, 4]

Drug / Food Interactions:
Food may decrease the absorption of norfloxacin. Food delays the absorption of ciprofloxacin, resulting in peak concentrations that are closer to two hours after dosing rather than one hour; however, overall absorption is not substantially affected.[2, 4] Dairy products such as milk and yogurt reduce the absorption of ciprofloxacin; therefore, avoid concurrent use. The bioavailability of ciprofloxacin may also be decreased by enteral feedings. Food delays the rate of absorption of lomefloxacin (time-to-reach maximum plasma concentration delayed by 41%, maximum concentration decreased by 18%) and decreases the extent of absorption (AUC) by 12%.

Table 4. Drug Interactions of the Quinolones[7]

Drug	Significance	Interaction	Mechanism
Quinolones	Level 2 Rapid onset, moderate severity, suspected	Quinolones (ciprofloxacin and norfloxacin) and **food**	Decreased GI absorption of quinolones resulting in decreased pharmacologic effects of quinolones.
Quinolones	Level 2 Rapid onset, moderate severity, suspected	Quinolones (ciprofloxacin, lomefloxacin, norfloxacin, ofloxacin) and **didanosine**	The magnesium and aluminum cations in the buffers present in didanosine tablets decrease GI absorption of quinolones via chelation, resulting in decreased effects of the quinolones.
Quinolones	Level 2 Rapid onset, moderate severity, probable	Quinolones (ciprofloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin) and **iron salts**	GI absorption of certain quinolones may be decreased by formation of an iron-quinolone complex, resulting in a decreased anti-infective response to quinolones.
Quinolones	Level 2 Delayed onset, moderate severity, suspected	Quinolones (ciprofloxacin, levofloxacin, norfloxacin, ofloxacin) and **anticoagulants**	Mechanism is unknown. The effect is an increased anticoagulant effect of warfarin.
Quinolones	Level 2 Rapid onset, moderate severity, probable	Quinolones (ciprofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin) and **sucralfate**	Decreased GI absorption of the quinolones causing decreased pharmacologic effects of the quinolones.
Quinolones	Level 2 Delayed onset, moderate severity, established	Quinolones (ciprofloxacin, norfloxacin) and **theophyllines**	Inhibition of hepatic metabolism of theophyllines leads to increased theophylline levels and toxicity can occur.
Quinolones	Level 2 Rapid onset, moderate severity, probable	Quinolones (all) and **antacids**	GI absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones.
Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) and **tricyclic antidepressants**	Mechanism is unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) and **antiarrhythmic agents**	Mechanism unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.

Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) and **phenothiazines**	Mechanism is unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) and **erythromycin** (cited in interaction reports)	Mechanism is unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) and **ziprasidone (Geodon)**	Mechanism is unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Quinolones	Level 1 Delayed onset, major severity, suspected	Quinolones (sparfloxacin) and **bepridil (Vascor)**	Mechanism is unknown. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Quinolones	Level 1 Delayed onset, moderate, suspected	Nalidixic acid and **anticoagulants**	Displacement of warfarin from binding sites on plasma proteins. The sustained nature of the interaction indicates another mechanism is also involved. The anticoagulant effects of warfarin may be enhanced by nalidixic acid.

VI. Adverse Drug Events of the Quinolones

In addition to the common adverse events reported in Table 6, both moxifloxacin and gatifloxacin have been shown to prolong the QTc interval and should not be used in patients with certain conditions or on drugs that may prolong the QT interval.

Table 5. Common Adverse Drug Events of the Quinolones

Adverse reaction		Cipro+[1]	Gati+	Levo+	Lome+	Moxi+	Nor+[2]	O+[1]	Spar+	Nalidixic Acid
CNS	Headache	1.2	3	0.1-6.4	3.6	2	2-2.8	1-9	4.2-8.1	√[4]
	Dizziness	< 1	3	0.3-2.7	2.1	3	1.7-2.6	1-5	2-3.8	√[4]
	Fatigue/Lethargy/Malaise	< 1		< 1-1.2	< 1	> 0.05-< 1	0.3-1	1-3	< 1	
	Somnolence/Drowsiness	< 1	< 0.1	< 1	< 1	> 0.05-< 1	0.3-1	1-3	< 1-1.5	
	Depression	< 1	< 0.1	< 1	< 1		0.1-0.2	< 1	< 1	
	Insomnia	< 1	= 0.1-< 3	0.5-4.6	< 1	> 0.05-< 1	0.3-1	3-7	1.9	
	Seizures/Convulsions[3]	< 1	< 0.1	< 1	< 1		√[4]	< 1		
	Confusion	=1	< 0.1	< 1	< 1	> 0.05-< 1	√[4]	< 1	< 1	
	Psychotic reactions	< 1					√[4]			
	Paresthesia	< 1	= 0.1-< 3	< 1	< 1		√[4]	< 1	< 1	
	Hallucinations	< 1	< 0.1	< 1		> 0.05-< 1		< 1	< 1	
Dermatologic	Photosensitivity[3]	< 1			2.3		√[4]	√[4]		√[4]
	Rash	1.1	= 0.1-< 3	0.3-1.2	< 1	> 0.05-< 1	0.3-1	1-3	1.1	√[4]
	Pruritus	< 1	< 0.1	0.4-1.3	< 1	> 0.05-< 1	0.3-1	1-3	1.8-3.3	√[4]

	Toxic epidermal necrolysis	< 1					√[4]			
	Stevens-Johnson syndrome	< 1					√[4]			
	Exfoliative dermatitis	< 1					√[4]			
	Hypersensitivity[3]	< 1			< 1		√[4]	√[3]		
GI	Nausea	5.2	8	1.3-7.2	3.5	8	2.6-4.2	3-10	4.3-7.6	√[4]
	Abdominal pain/discomfort/cramping	= 1-1.7	= 0.1-< 3	0.4-2.5	1.2	> 0.05-= 2	0.3-1.6	1-3	1.8-2.4	√[4]
	Diarrhea	2.3	4	1-5.6	1.4	6	0.3-1	1-4	3.2-4.6	√[4]
	Vomiting	= 1-2	= 0.1-< 3	0.2-2.3	< 1	2	0.3-1	1-4	< 1-1.3	√[4]
	Dry/painful mouth	< 1		< 1	< 1	> 0.05-< 1	0.3-1	1-3	< 1-1.4	
	Dyspepsia/Heartburn	< 1	=0.1-< 3	0.3-2.4	< 1	1	0.3-1	< 1	1.6-2.3	
	Constipation	< 1	=0.1-< 3	0.1-3.2	< 1	> 0.05-< 1	0.3-1	1-3	< 1	
	Flatulence	< 1	< 0.1	0.4-1.5	< 1		0.3-1	1-3	< 1-1.1	
	Pseudomembranous colitis[3]	< 1	< 0.1	< 1	√[4]		√[4]	√[3]		
Miscellaneous	Visual disturbances	< 1			< 1		0.1-0.2	1-3		√[4]
	Hearing loss	< 1					√[4]	< 1		
	Vaginitis	< 1	6	0.7-1.8	< 1	> 0.05-< 1		1-5	< 1	
	Hypertension	< 1	< 0.1	< 1	< 1	> 0.05-< 1		< 1	< 1	
	Palpitations	< 1	= 0.1-< 3	< 1		> 0.05-< 1		< 1	< 1	
	Syncope	< 1		< 1	< 1			< 1		
	Chills	< 1	= 0.1-< 3		< 1	> 0.05-< 1	0.1-0.2	< 1	< 1	
	Edema	< 1	< 0.1	< 1	< 1		0.1-0.2	< 1		
	Fever	< 1	= 0.1-< 3	< 1			0.3-1	1-3	< 1	
Abnormal laboratory values	↑ALT/↑ AST	1.9/1.7	< 1		=0.4		1.4/1.4-1.6	= 1	2-2.3	
	↑Alkaline phosphatase	0.8	< 1		0.1		1.1	= 1	< 1	
	↑LDH	0.4		< 1			√[4]			
	↑or ↓Bilirubin	0.3	< 1		0.1	=2			< 1	
	Eosinophilia	0.6			0.1	> 0.05-< 1	0.6-1.5	= 1		√[4]
	Leukopenia	0.4		< 1	0.1	> 0.05-< 1	1.4	= 1		√[4]
	↑or ↓Platelets	0.1			< 1		1		< 1	√[4]
	Pancytopenia	0.1								
	↑ESR/Lymphocytopenia				< 0.1			= 1		
	Neutropenia		< 1				1.4	= 1		
	↑Serum creatinine	1.1			0.1		√[4]	= 1		

	↑BUN	0.9			0.1		√4	= 1		
	Crystalluria/Cylinduria/ Candiduria	√4					√4			
	Hematuria	√4						= 1		
	Glucosuria/Pyuria						√4	=		
	Proteinuria/Albuminuria				< 0.1		1	= 1		
	↑ -glutamyltransferase	< 0.1			< 0.1					
	↑Serum amylase	< 0.1	< 1						< 1	
	↑Uric acid	< 0.1								
	↑or ↓Blood glucose	< 0.1		2.2	< 0.1			= 1	< 1	
	↓ Hemoglobin/Hematocrit	< 0.1			< 0.1	= 2	0.6			
	↑or ↓Potassium	√4			0.1				< 1	
	Anemia	< 0.1			< 0.1			= 1		√4
	Bleeding/ ↑ PT	< 0.1			< 0.1					
	↑Monocytes	< 0.1			0.2				< 1	
	Leukocytosis	< 0.1		< 1	0.1			=		
	↑ Triglycerides/Cholesterol	√4								

[1]Includes data for oral and IV formulations.
[2]From single- and multiple-dose studies.
[3]See Warnings or Precautions.
√4 = Adverse reaction observed; incidence not reported.
+ = floxacin

VII. Dosing and Administration for the Quinolones

Table 6 illustrates dosing of the different quinolones. Appendix A (before References) has been created to display dosing tables for drugs with extensive indications and dosing recommendations.

Table 6. Dosing for the Quinolones[1-4]

Drug	Availability	Dose /Frequency/Duration
Ciprofloxacin	Tablets: 100 (cystitis pack), 250, 500, and 750mg Extended-release tablets: 500 and 1000mg Powder for oral suspension: 250mg/5mL, 500mg/5mL Injection: 200 and 400mg; also 200 and 400mg in 5% dextrose	XR tablets may be taken with meals that include milk; however, avoid coadministration with dairy products alone or with calcium-fortified products because decreased absorption is possible.[4] A two-hour window between substantial calcium intake (more than 800mg) and dosing with XR tablets is recommended. Swallow the XR tablet whole; do not split, crush, or chew. XR and IR tablets are not interchangeable. Administer ciprofloxacin at least two hours before or six hours after magnesium/aluminum antacids, sucralfate, didanosine chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron, or zinc. The duration of treatment depends upon the severity of infection. Generally, continue ciprofloxacin for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections, more prolonged therapy may be required. Bone and joint infections may require treatment for at least four to six weeks. Infectious diarrhea may be treated for five to seven days. Treat typhoid fever for ten days. Treat chronic bacterial prostatitis for 28 days. See Appendix A for detailed dosing recommendations.

<table>
<tr>
<td>Gatifloxacin</td>
<td>Tablets: 200 and 400mg
Injection: 10mg/mL concentrate
200 and 400mg premix</td>
<td>Administer gatifloxacin without regard to food, including milk and dietary supplements containing calcium. Administer once every 24 hours. Also administer oral gatifloxacin at least four hours before the administration of ferrous sulfate; dietary supplements containing zinc, magnesium, or iron (such as multivitamins); aluminum/magnesium-containing antacids; or didanosine buffered tablets, buffered solution, or buffered powder for oral suspension.

When switching from IV to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with the injection may be switched to tablets when clinically indicated.

<table>
<tr><th colspan="3">Gatifloxacin Dosage Guidelines[4]</th></tr>
<tr><th>Infection[1]</th><th>Daily dose (mg)[2]</th><th>Duration</th></tr>
<tr><td>Acute bacterial exacerbation of chronic bronchitis</td><td>400</td><td>5 days</td></tr>
<tr><td>Acute sinusitis</td><td>400</td><td>10 days</td></tr>
<tr><td>Community-acquired pneumonia</td><td>400</td><td>7 to 14 days</td></tr>
<tr><td>Uncomplicated skin and skin structure infections</td><td>400</td><td>7 to 10 days</td></tr>
<tr><td rowspan="2">Uncomplicated UTIs (cystitis)</td><td>400</td><td>Single dose</td></tr>
<tr><td>or 200</td><td>3 days</td></tr>
<tr><td>Complicated UTIs</td><td>400</td><td>7 to 10 days</td></tr>
<tr><td>Acute pyelonephritis</td><td>400</td><td>7 to 10 days</td></tr>
<tr><td>Uncomplicated urethral gonorrhea in men; endocervical and rectal gonorrhea in women</td><td>400</td><td>Single dose</td></tr>
</table>
[1]Caused by the designated pathogens (see Indications).
[2]For oral or IV routes of administration.</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Tablets: 250, 500, 750mg
Solution: 25mg/ml
Injection: 25mg/ml concentrate
Injection: 250, 500, and 750mg premix</td>
<td>Usual dose of the tablets/injection is 250mg or 500mg administered orally or by slow infusion over 60 minutes every 24 hours, or 750mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing table.[4] Administer oral doses at least two hours before or two hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron and multivitamin preparations with zinc, or didanosine (chewable/buffered tablets or pediatric powder for oral solution).

<table>
<tr><th colspan="5">Levofloxacin Dosing with Normal Renal Function[4]
(CCl > 80 mL/min)</th></tr>
<tr><th>Infection[1]</th><th>Unit dose</th><th>Frequency</th><th>Duration[2]</th><th>Daily dose</th></tr>
<tr><td>Acute bacterial exacerbation of chronic bronchitis</td><td>500mg</td><td>Q 24 h</td><td>7 days</td><td>500mg</td></tr>
<tr><td>Acute maxillary sinusitis</td><td>500mg</td><td>Q 24 h</td><td>10 to 14 days</td><td>500mg</td></tr>
<tr><td>Acute pyelonephritis</td><td>250mg</td><td>Q 24 h</td><td>10 days</td><td>250mg</td></tr>
<tr><td>Chronic bacterial prostatitis</td><td>500mg</td><td>Q 24 h</td><td>28 days</td><td>500mg</td></tr>
<tr><td rowspan="2">Pneumonia, community-acquired</td><td>500mg</td><td>Q 24 h</td><td>7 to 14 days</td><td>500mg</td></tr>
<tr><td>750mg[3]</td><td>Q 24 h</td><td>5 days</td><td>750mg</td></tr>
<tr><td>Pneumonia, nosocomial</td><td>750mg</td><td>Q 24 h</td><td>7 to 14 days</td><td>750mg</td></tr>
<tr><td>SSSI, complicated</td><td>750mg</td><td>Q 24 h</td><td>7 to 14 days</td><td>750mg</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>UTI, complicated</td><td>250mg</td><td>Q 24 h</td><td>10 days</td><td>250mg</td></tr>
<tr><td>UTI, uncomplicated</td><td>250mg</td><td>Q 24 h</td><td>3 days</td><td>250mg</td></tr>
</table>
[1]Caused by the designated pathogens (see Indications).
[2]Sequential therapy (IV to oral) may be instituted at the discretion of the physician.
[3]Efficacy of this alternat ive regimen has only been documented for infections caused by penicillin -susceptible S. pneumoniae, H. influenzae, H. parainfluenzae, M. pneumoniae, and C. pneumoniae.
</td></tr>
<tr><td>Lomefloxacin</td><td>Tablets: 400mg</td><td>
Risk of reaction to solar UVA light may be reduced by taking lomefloxacin at least 12 hours before exposure to the sun (e.g., in the evening). Lomefloxacin may be taken without regard to meals. Sucralfate and antacids containing magnesium or aluminum, or didanosine chewable/buffered tablets or the pediatric powder for oral solution should not be taken within four hours before or two hours after taking lomefloxacin.
<table>
<tr><td colspan="5">Recommended Daily Dose of Lomefloxacin[4]</td></tr>
<tr><td>Body System</td><td>Infection</td><td>Dose</td><td>Frequency</td><td>Duration</td></tr>
<tr><td>Lower respiratory tract</td><td>Acute bacterial exacerbation of chronic bronchitis</td><td>400mg</td><td>once daily</td><td>10 days</td></tr>
<tr><td>Urinary tract</td><td>Uncomplicated cystitis caused by K. pneumoniae, P. mirabilis, or S. saprophyticus</td><td>400mg</td><td>once daily</td><td>10 days</td></tr>
<tr><td></td><td>Uncomplicated cystitis in females caused by E. coli</td><td>400mg</td><td>once daily</td><td>3 days</td></tr>
<tr><td></td><td>Complicated UTI</td><td>400mg</td><td>once daily</td><td>14 days</td></tr>
</table>
</td></tr>
<tr><td>Moxifloxacin</td><td>Tablets: 400mg
Injection: 400mg premix</td><td>
<table>
<tr><td colspan="4">Moxifloxacin Dosage Guidelines[4]</td></tr>
<tr><td>Infection[1]</td><td>Daily dose (mg)</td><td>Frequency</td><td>Duration (days)</td></tr>
<tr><td>Acute bacterial sinusitis</td><td>400</td><td>q 24 h</td><td>10</td></tr>
<tr><td>Acute bacterial exacerbation of chronic bronchitis</td><td>400</td><td>q 24 h</td><td>5</td></tr>
<tr><td>Community-acquired pneumonia</td><td>400</td><td>q 24 h</td><td>7 to 14</td></tr>
<tr><td>Uncomplicated skin and skin structure infections</td><td>400</td><td>q 24 h</td><td>7</td></tr>
</table>
[1]Caused by the designated pathogens (see Indications).

Administer oral doses of moxifloxacin at least four hours before or eight hours after antacids containing magnesium or aluminum, sucralfate, metal cations such as iron, multivitamin preparations with zinc, or didanosine (chewable/buffered tablets or pediatric powder for oral solution).

Moxifloxacin may be administered without regard to food.

Switching from IV to oral dosing: When switching from IV to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with IV moxifloxacin may be switched to the oral dosage form when clinically indicated at the discretion of the physician.
</td></tr>
</table>

<table>
<tr>
<td>Norfloxacin</td>
<td>Tablets: 400mg</td>
<td>Take = 1 hour before or = 2 hours after meals or ingestion of milk or other dairy products. Take with a glass of water. Hydrate patients well.

<table>
<tr><th colspan="6">Recommended Norfloxacin Dosage</th></tr>
<tr><th>Infection</th><th>Description</th><th>Dose</th><th>Frequency</th><th>Duration</th><th>Daily dose</th></tr>
<tr><td>Urinary tract infections (UTI)</td><td>Uncomplicated (cystitis) due to E. coli, K. pneumoniae, or P. mirabilis</td><td>400mg</td><td>q 12 h</td><td>3 days</td><td>800mg</td></tr>
<tr><td></td><td>Uncomplicated due to other indicated organisms</td><td>400mg</td><td>q 12 h</td><td>7-10 days</td><td>800mg</td></tr>
<tr><td></td><td>Complicated</td><td>400mg</td><td>q 12 h</td><td>10-21 days</td><td>800mg</td></tr>
<tr><td>Sexually transmitted diseases</td><td>Uncomplicated gonorrhea</td><td>800mg</td><td>single dose</td><td>1 day</td><td>800mg</td></tr>
<tr><td>Prostatitis</td><td>Acute or chronic</td><td>400mg</td><td>q 12 h</td><td>28 days</td><td>800mg</td></tr>
</table>
</td>
</tr>
<tr>
<td>Nalidixic Acid</td>
<td>Caplets: 250mg, 500mg, and 1gram
Suspension: 250mg/5mL</td>
<td>Underdosage (< 4g/day) during initial treatment may predispose to emergence of bacterial resistance.
Adults:
Initial therapy:
1g 4 times/day (total dose 4 g/day) for 1 or 2 weeks.
Prolonged therapy:
May be reduced to 2g/day after the initial treatment period.
Children (3 months to = 12 years of age):
Initial therapy:
55mg/kg/day (25mg/lb/day) in 4 equally divided doses.
Prolonged therapy:
May be reduced to 33mg/kg/day (15 mg/lb/day).

Do not administer to infants < 3 months of age.</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Tablets: 200, 300, and 400mg</td>
<td>
<table>
<tr><th colspan="6">Ofloxacin Dosage Guidelines [1, 4]</th></tr>
<tr><th>Infection</th><th>Description</th><th>Dose</th><th>Frequency</th><th>Duration</th><th>Daily dose</th></tr>
<tr><td>Lower respiratory tract</td><td>Exacerbation of chronic bronchitis</td><td>400mg</td><td>q 12 h</td><td>10 days</td><td>800mg</td></tr>
<tr><td></td><td>Community acquired pneumonia</td><td>400mg</td><td>q 12 h</td><td>10 days</td><td>800mg</td></tr>
<tr><td>Sexually transmitted diseases</td><td>Acute, uncomplicated urethral and cervical gonorrhea</td><td>400mg</td><td>single dose</td><td>1 day</td><td>400mg</td></tr>
<tr><td></td><td>Cervicitis/urethritis due to C. trachomatis</td><td>300mg</td><td>q 12 h</td><td>7 days</td><td>600mg</td></tr>
<tr><td></td><td>Cervicitis/urethritis due to C. trachomatis and N. gonorrhoeae</td><td>300mg</td><td>q 12 h</td><td>7 days</td><td>600mg</td></tr>
<tr><td></td><td>Acute pelvic inflammatory disease</td><td>400mg</td><td>q 12 h</td><td>10 to 14 days</td><td>800mg</td></tr>
<tr><td>Skin and skin structure</td><td>Uncomplicated</td><td>400mg</td><td>q 12 h</td><td>10 days</td><td>800mg</td></tr>
</table>
</td>
</tr>
</table>

		<table><tr><td>Urinary tract</td><td>Uncomplicated cystitis due to *E. coli* or *K. pneumoniae*</td><td>200 mg</td><td>q 12 h</td><td>3 days</td><td>400mg</td></tr><tr><td></td><td>Uncomplicated cystitis due to other organisms</td><td>200mg</td><td>q 12 h</td><td>7 days</td><td>400mg</td></tr><tr><td></td><td>Complicated UTIs</td><td>200mg</td><td>q 12 h</td><td>10 days</td><td>400mg</td></tr><tr><td>Prostatitis</td><td>Due to *E. coli*</td><td>300mg</td><td>q 12 h</td><td>6 weeks</td><td>600mg</td></tr></table>[1]Due to the designated pathogens (see Indications). Do not take antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; multivitamins containing zinc; or didanosine chewable/buffered tablets or the pediatric powder for oral solution 2 hours before or 2 hours after taking ofloxacin. CDC Recommended Treatment Schedules ***Chlamydia:*** 300mg orally 2 times a day for 7 days (alternative regimen). ***Epididymitis:*** 300mg orally 2 times a day for 10 days. ***PID, outpatient:*** 400mg orally 2 times a day for 14 days plus metronidazole. ***Gonococcal infections, uncomplicated:*** 400mg orally in a single dose plus doxycycline or azithromycin.
Sparfloxacin	Tablet: 200mg	Sparfloxacin can be taken with or without food. Antacids containing magnesium or aluminum or sucralfate or didanosine chewable/buffered tablets or the pediatric powder for oral solution may be taken four hours after sparfloxacin administration. The recommended daily dose of sparfloxacin in patients with normal renal function is two 200mg tablets taken on the first day as a loading dose. Thereafter, take one 200mg tablet every 24 hours for a total of 10 days of therapy (11 tablets).

Special Dosing Considerations

Table 7. Special Dosing Considerations for the Quinolones[1-4]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category[8]	Can Drug Be Crushed?
Ciprofloxacin	Yes	No	Safety and efficacy not established in children and adolescents <18. The benefits may outweigh the risk for conditions such as anthrax exposure and in those age 9-18 with serious infections, whose skeletal growth is complete.	C	Oral suspension is available for alternative administration, however, it cannot be administered through feeding tubes due to its physical characteristics. The extended-release tablets should not be crushed.
Gatifloxacin	Yes	No	Safety and efficacy are not established in children or adolescents younger than 18 years of age.	C	Per manufacturer, no studies have evaluated the bioavailability of the tablets when crushed or when given per tube. The manufacturer does not anticipate problems with crushing the tablets as they are film-coated.

Levofloxacin	Yes	No	Safety and effectiveness in pediatric patients and adolescents below the age of 18 years has not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species.	C	Levofloxacin tablets are not scored, but are film-coated, and can be crushed, mixed with water, and given per tube. The oral solution has not been specifically studied for feeding tube administration.
Lomefloxacin	Yes	No	Safety and efficacy of lomefloxacin in children younger than 18 years of age has not been established. Caution should be used in adolescents if skeletal growth isn't complete.	C	Per manufacturer, lomefloxacin has not been specifically studied when crushed or given per tube. However, the drug is scored and can be broken in half; therefore, the manufacturer does not anticipate proble ms with crushing the drug per tube.
Moxifloxacin	No	No	Safety and efficacy in pediatric patients and adolescents less than 18 years of age have not been established. Moxifloxacin has caused arthropathy in juvenile animals.	C	Moxifloxacin tablets are not scored, but are available as film-coated tablets. No problems would be anticipated when crushing the film-coated tablets.
Norfloxacin	Yes	No	Safety and efficacy of oral norfloxacin in pediatric patients and adolescents below the age of 18 years have not been established. Norfloxacin causes arthropathy in juvenile animals of several animal species.	C	Norfloxacin tablets are film-coated; therefore, problems would not be anticipated when crushing the film-coated tablets.
Nalidixic Acid	No	No	Do not administer to infants <3 months of age.	B	Nalidixic acid caplets are scored; therefore, they can be broken and crushed for alternative administration.
Ofloxacin	Yes	Cirrhosis - do not exceed 400mg/day	Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy and osteochondrosis in juvenile animals of several species.	C	Ofloxacin tablets are available film-coated, but are not scored. No problems would be anticipated when crushing the film-coated tablets.
Sparfloxacin	Yes	No	The safety and effectiveness of sparfloxacin in adolescents and children under 18 years of age have not been established. Fluoroquinolones cause arthropathy and osteochondrosis in juvenile animals of several species.	C	Sparfloxacin tablets are available film-coated. No problems would be anticipated when crushing the film-coated tablets.

VIII. Comparative Effectiveness of the Quinolones

Table 8. Additional Outcomes Evidence for the Quinolones

Study	Sample	Treatment / Duration	Results
Tarshis G, et al.[9] Randomized, double blind, multicenter study of levofloxacin vs. gatifloxacin	n=407	Levofloxacin 500mg QD for 7-10 days or gatifloxacin 400mg QD for 7-10 days	**Primary Endpoints** Clinical cure rates; bacterial eradication rates; adverse events. **Efficacy: levofloxacin=gatifloxacin** • The cure rates were 91% [146 of 161] for gatifloxacin and 84% [145 of 161] for levofloxacin (95% confidence interval [CI] for the difference, -2.0 to 15.2%). • Clinical cure rates for microbiologically evaluable patients were 93% [88 of 95] for gatifloxacin and 88% [75 of 85] for levofloxacin (95% CI for the difference, -6.5 to 16.8%). • The bacterial eradication rate was 92% for each group, with gatifloxacin eradicating 93% of the methicillin-susceptible *Staphylococcus aureus* isolates and levofloxacin eradicating 91% of them. • The eradication rates for gatifloxacin and levofloxacin were 91% each for patients infected with gram positive aerobes and 94 and 93%, respectively, for patients infected with gram-negative aerobes. • Findings from this study indicate that gatifloxacin is at least as clinically and microbiologically effective as levofloxacin for the treatment of patients with uncomplicated skin or soft tissue infections, including those whose infections are due to *S. aureus* or *S. pyogenes.* **Safety: levofloxacin=gatifloxacin** • A minority of patients discontinued the study drug prematurely due to a drug-related event (two gatifloxacin-treated and nine levofloxacin-treated patients). • Most common adverse events: nausea, diarrhea, vaginitis, dizziness, abdominal pain, headache, pruritus, asthenia, rash, nervousness, eructation and pain.
Cox CE, et al.[10] Randomized, double blind, multicenter study of gatifloxacin vs. ciprofloxacin	n=372	Gatifloxacin 400mg QD for 7-10 days or ciprofloxacin 500mg BID for 7-10days	**Primary Endpoints** Clinical response rates; pathogen eradication rates; sustained eradication rates; adverse events. **Efficacy: gatifloxacin=ciprofloxacin** • Pathogen eradication rates for complicated UTIs were 92% and 83% with gatifloxacin and ciprofloxacin, respectively (95% CI, -4.1% to 24.5%). For pyelonephritis, the respective rates were 92% and 85% (95% CI, -20% to 37%). • Clinical response rates of >90% were observed in both treatment groups among patients with complicated UTIs as well as those with pyelonephritis. • Sustained eradication rates were 76% (64/84) with gatifloxacin and 66% (52/79) with ciprofloxacin. • Gatifloxacin was comparable to ciprofloxacin based on clinical efficacy and bacteriologic eradication rates for the treatment of complicated urinary tract infections or pyelonephritis. **Safety: gatifloxacin=ciprofloxacin** Overall, 22 patients discontinued treatment because of adverse events: 12 patients in the gatifloxacin group and 10 patients in the ciprofloxacin group. Most common adverse events: nausea, dizziness, diarrhea, and vomiting.
Lipsky BA, et al.[11] Randomized, double blind, multicenter study of sparfloxacin vs. ciprofloxacin	n=475	Sparfloxacin 400mg Day 1, then 200mg QD for 9 days or ciprofloxacin 750mg BID for 10 days	**Primary Endpoints** Clinical success rates (% of patients cured or improved); bacteriologic success rates; adverse events. **Efficacy: sparfloxacin=ciprofloxacin** • The clinical success rate was 90.1% (210/233) with sparfloxacin and 87.2% (211/233) with ciprofloxacin [95% confidence interval, -2.8 to 8.6]. • The bacteriologic success rates were 87.0% (141/161) with sparfloxacin and 79.9% (123/154) with ciprofloxacin [95% CI, -1 to 15.3]. • Eradication rates of *S. aureus* and coagulase-negative staphylococcal infections were 90.2% (101/112) with sparfloxacin and 77.9% (88/113) for ciprofloxacin.

			• For patients with two or more pathogens at baseline (mixed infections), bacteriologic success was 87.6% for sparfloxacin and 77.9% for ciprofloxacin. • *Pseudomonas aeruginosa* infections were eradicated or presumed eradicated in 71.4% (10/14) of the sparfloxacin-treated patients and 87.5% (7/8) of ciprofloxacin-treated patients. • The efficacy of sparfloxacin was comparable to that of ciprofloxacin in the treatment of community-acquired, complicated skin and skin-structure infections, including those caused by staphylococci, the most common pathogens. **Safety: sparfloxacin =ciprofloxacin** • The percentages of patients reporting adverse events considered to be possibly or probably related to study medication were 26.5% (79/298) and 23.3% (71/305) in the sparfloxacin and ciprofloxacin treatment groups, respectively. • The most common adverse drug related events were nausea, photosensitivity reaction, diarrhea, and vomiting, which occurred in 3.4%, 11.1%, 3.4% and 0.3% of patients, respectively, in the sparfloxacin group and in 12.1%, 0.7%, 4.9% and 2.0% of patients, respectively, in the ciprofloxacin group. • Drug related adverse events involving the digestive system occurred in 7.1% of sparfloxacin-treated patients and 19% of ciprofloxacin treated patients. • Photosensitivity reactions were reported in 11.1% of patients in the sparfloxacin group and 0.7% of patients in the ciprofloxacin group ($p<0.001$). • The mean change in QT_c interval from baseline to the maximum on treatment value was greater in the sparfloxacin group (9 milliseconds) than in the ciprofloxacin group (3 milliseconds) (p=0.005; 95%CI, 0.002 to 0.010).
Greenberg RN, et al. [12] Randomized, double blind, multicenter study of gatifloxacin vs. ofloxacin	n=728	Gatifloxacin 400mg or 600mg once or ofloxacin 400mg once	**Primary Endpoints** Bacteriologic eradication rates; symptomatic improvement; adverse events. **Efficacy: gatifloxacin=ofloxacin** • Bacteriologic eradication rates for gatifloxacin in evaluable men with urethral gonorrhea were 99% (400mg) and 100%(600mg) versus 100% for ofloxacin (n=117,122, and 55, respectively; p=ns). • Eradication rates in evaluable women with endocervical gonorrhea were 99% for both 400mg and 600mg gatifloxacin versus 100% for ofloxacin (n=101, 104, and 55, respectively; p=ns). • Eradication rates were 100% for both rectal (n=43) and pharyngeal (n=31) infection across all treatment groups. • Symptomatic improvement was noted in 96% of male patients (278 of 290 patients) and in 73% of female patients (155 of 211 patients) at follow up on day 4 to day 10. • These findings suggest that a single dose of gatifloxacin or ofloxacin is a useful first-line agent for the treatment of uncomplicated genitourinary, pharyngeal or anorectal infection with *N. gonorrhoeae*. **Safety: gatifloxacin=ofloxacin** • Most common adverse events were gastrointestinal intolerance (nausea, diarrhea, vomiting or abdominal pain), headache, dizziness, nonmonilial vaginitis, vaginal candidiasis. • Slightly fewer drug-related adverse events were seen among patients taking 400mg gatifloxacin relative to those receiving 600mg gatifloxacin (22% versus 26%).
Henry DC, et al. [13] Randomized, double blind, multicenter trial of sparfloxacin vs. ciprofloxacin	n=1,175	Single dose sparfloxacin regimen, given as a 400mg dose on the morning of day 1 and placebo given for 6 more days vs. three day sparfloxacin regimen, given as a 400mg loading dose on day 1, followed by 200mg/d on the	**Primary Endpoints** Clinical success (5-9 days after therapy); sustained clinical success (4-6 weeks after therapy); bacteriologic eradication rates; clinical recurrence rate; bacteriologic recurrence; adverse events. **Efficacy: sparfloxacin=ciprofloxacin** • In all treated populations, clinical success was achieved five to nine days after therapy in 91.8%, 92.2%, and 91.6% of patients in the single-dose sparfloxacin, three-day sparfloxacin, and seven-day ciprofloxacin groups respectively; bacteriologic success rates were 80.7%, 90.1% and 92.6% of those in the three groups. • Sustained clinical success rates four to six weeks after therapy were 76.6%,

		morning of days 2-3 and placebo on days 4-7 vs. seven day ciprofloxacin regimen given as a 250mg tablet BID for 7 days	80.2%, and 79.5% in the single-dose sparfloxacin, 3-day sparfloxacin and 7-day ciprofloxacin groups respectively; sustained bacteriologic success rates were 80.7%, 90.1% and 92.6%. • Patients in the single-dose sparfloxacin group had a clinical recurrence rate of 12.0% and a bacteriologic relapse rate of 14.3% compared with patients in the 3-day sparfloxacin (8.1% and 3.9%, respectively) and 7-day ciprofloxacin (7.7% and 6.5%, respectively). • The 3-day sparfloxacin regimen was equivalent to a seven-day, twice daily regimen of ciprofloxacin in terms of other measures of effectiveness, such as sustained clinical and overall success rates. **Safety: sparfloxacin < ciprofloxacin** • Most common adverse events were nausea, headache, vaginal candidiasis, dizziness, pruritis, photosensitivity reaction, somnolence, dyspepsia and diarrhea. Adverse events were comparable with the exception of photosensitivity. • Photosensitivity occurred in 3.3% of the 3-day sparfloxacin group, 1.3% of the single dose sparfloxacin group, and 0.3% of the ciprofloxacin group (p=0.005).
Dunbar LM, et al.[14] Randomized, double-blind, multicenter trial of levofloxacin in community-acquired pneumonia	n=390	Levofloxacin 500mg once daily for 10 days or levofloxacin 750 mg once daily for 5 days	**Endpoints** Clinical response Microbiological eradication rate **Efficacy: levofloxacin 500 mg x 10 days = 750 mg x 5 days** • The clinical success rates were 92.4% (183 of 198 persons) for the 750-mg group and 91.1% (175 of 192 persons) for the 500-mg group (95% confidence interval, -7.0 to 4.4). • Microbiologic eradication rates were 93.2% and 92.4% in the 750-mg and 500-mg groups, respectively. **Safety: Levofloxacin 500 mg x 10 days = 750 mg x 5 days**
Auquer F, et al.[15] Randomized, double-blind study of ciprofloxacin and norfloxacin for uncomplicated UTI in women	n=226	Ciprofloxacin 500mg x1 vs. 400mg BID of norfloxacin x 3 days	**Primary Endpoints** Clinical and microbiological outcome at day seven. **Efficacy: ciprofloxacin = norfloxacin** • Bacteriologic cure was 91.2% for the ciprofloxacin group and 91.9% in the norfloxacin group. • Clinical resolution was 91.2% and 93.8%, respectively. • Both treatments were equally efficacious (p=0.016).
Klimberg IW, et al.[16] Randomized, double-blind, multicenter study of levofloxacin vs. lomefloxacin	n=336	Levofloxacin 250mg QD for 7-10 days or lomefloxacin 400mg QD for 14 days	**Primary Endpoints** Safety and microbiologic efficacy for treatment of complicated urinary tract infections. **Efficacy: levofloxacin = lomefloxacin** • The overall microbiologic eradication rate of pathogens was 95.5% (168 of 176) for levofloxacin and 91.7% (154 of 168) for lomefloxacin. • Eradication rates with respect to patients were 95.3% (163 of 171) and 92.1% (152 of 165) for levofloxacin and lomefloxacin, respectively. • At the five to nine-day post-therapy visit, symptoms were completely resolved in 84.8% of levofloxacin-treated patients and were decreased in 8.2% (93.0% clinical success). Among the lomefloxacin-treated patients, complete resolution was seen in 82.4%, with decreased symptoms in 6.1% (88.5% clinical success). **Safety: levofloxacin > lomefloxacin** • Drug-related adverse events (AEs) were reported by 10 (2.6%) and 18 (5.2%) levofloxacin- and lomefloxacin-treated patients, respectively. • Compared with levofloxacin-treated patients, more lomefloxacin-treated patients experienced photosensitivity reactions (3 [1.3%] versus 0) and dizziness (2 [0.9%] versus 0). • Nausea (3 [1.3%] versus 1 [0.4%]) was more frequent in the levofloxacin-treated group. • Six patients in each treatment group had a gastrointestinal AE (1.7%); rash was reported more frequently with lomefloxacin (four patients [0.4%]) than with levofloxacin (one patient [0.4%]). • Discontinuation because of AEs was observed in eight (3.4%) levofloxacin- and 14 (6.1%) lomefloxacin-treated patients.

Nicodemo AC, et al.[17] Randomized, double-blind study comparing oral levofloxacin vs. ciprofloxacin for uncomplicated skin and skin structure infections	n=253	Levofloxacin 500mg QD for 7 days vs. ciprofloxacin 500mg BID for 10 days	**Primary Endpoints** Bacteriological eradication rates by pathogen, and clinical success. **Efficacy: levofloxacin=ciprofloxacin** • Clinical success (cure and improvement) was observed in 96.1% of levofloxacin-treated patients and in 93.5% of ciprofloxacin-treated patients. • Overall, bacteriological eradication rates by pathogen were 93.2% and 91.7%, respectively. • Levofloxacin eradicated 94% (66/70) of Staphylococcus aureus and 94% (17/18) of Streptococcus pyogenes isolates, compared with 93% (70/75) and 92% (12/13) for ciprofloxacin. • Microbiological eradication rates by subject were approximately 93% and 90% for the levofloxacin and ciprofloxacin groups, respectively. **Safety: levofloxacin=ciprofloxacin** • Drug-related adverse events were reported by 8.9% of those receiving levofloxacin and 8.2% of those administered ciprofloxacin.
Polubiec A, et al.[18] Randomized study of ciprofloxacin vs. ofloxacin for lower respiratory tract infections	n=100	Ciprofloxacin 250mg BID or ofloxacin 200mg BID given for 10-12 days	**Primary Endpoints** Microbiological sputum cure. **Efficacy: ciprofloxacin=ofloxacin** • In both groups, the clinical results were considered to be excellent, with clinical cure in 98% of the patients treated with ciprofloxacin and in 90% of patients treated with ofloxacin. • Eradication of the initial sputum isolate was achieved in 98% of the patients of the ciprofloxacin group and in 82% of the patients of the ofloxacin group.
Richard GA, et al.[19] Two randomized, multicenter trials of levofloxacin vs. ciprofloxacin vs. lomefloxacin in acute pyelonephritis	n=186	Levofloxacin 250mg QD, ciprofloxacin 500mg BID, or lomefloxacin 400mg QD	**Primary Endpoints** Microbiologic response measured by microbiologic efficacy. **Efficacy: ciprofloxacin=levofloxacin=lomefloxacin** • At five to nine days after the end of treatment, 95% of uropathogens were eradicated in patients who received levofloxacin compared with 94% in the ciprofloxacin-treated group and 95% in the lomefloxacin-treated group. • The clinical cure rate was 92% for levofloxacin in both studies combined, 88% for ciprofloxacin, and 80% for lomefloxacin. • Drug-related adverse events were reported by 2% of levofloxacin-treated patients, 8% of ciprofloxacin-treated patients, and 5% of lomefloxacin-treated patients.
Richard GA, et al.[20] Randomized, double-blind study of single-dose vs. 3-day quinolone therapy in acute uncomplicated UTI	-	Gatifloxacin 400mg x1 vs. gatifloxacin 200mg QD x 3 days vs. ciprofloxacin 100mg BID for 3 days	**Primary Endpoints** Bacterial eradication rate, clinical efficacy rate. **Efficacy: Single-dose and 3-day gatifloxacin=3-day ciprofloxacin** • The bacterial eradication rate for the single-dose gatifloxacin, 3-day gatifloxacin, and 3-day ciprofloxacin groups was 90%, 95%, and 89%, respectively; the clinical efficacy rate was 93%, 95%, and 93%, respectively, for microbiologically assessable patients at the test-of-cure visit. • Eradication of the most common uropathogens, including *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*, was achieved with gatifloxacin and ciprofloxacin. • Single-dose gatifloxacin was equivalent to 3-day ciprofloxacin in both microbiologic and clinical efficacy.
Greenberg RN, et al.[21] Ciprofloxacin, lomefloxacin, and levofloxacin in the treatment of chronic osteomyelitis	n=27	-	**Primary Endpoints** Efficacy of the therapy **Efficacy:** • Levofloxacin was effective therapy for 9 of 15 (60%) patients. Lomefloxacin was effective therapy for five of seven (71%) patients, and ciprofloxacin was effective therapy for two of five patients (40%). • Average follow-up was 11.8 months for patients who completed the course of therapy, and the average duration of therapy was 60.6 days. • Gram-positive bacteria were isolated from 18 patients, and 11 patients were cured. • Summary: Oral fluoroquinolones can be safe, effective therapy if they are given for a prolonged course as treatment for infections caused by susceptible gram-positive as well as gram-negative organisms and in combination with adequate surgical debridement.
Bundrick W, et al.[22]	n=377	Levofloxacin 500mg QD or ciprofloxacin	**Primary Endpoints** Microbiologic efficacy in the microbiologically assessable population

Randomized, double-blind, multicenter study of levofloxacin vs. ciprofloxacin for chronic bacterial prostatitis		500mg BID for 28 days	**Efficacy: levofloxacin=ciprofloxacin** • The clinical success rates, including cured plus improved patients, were similar (75% for levofloxacin and 72.8% for ciprofloxacin; 95% confidence interval for the difference in the success rates: -13.27 to 8.87), as were the microbiologic eradication rates (75% for levofloxacin and 76.8% for ciprofloxacin; 95% confidence interval for the difference -8.98 to 12.58). • Enterococcus faecalis and Escherichia coli were the most common isolates. • The 6-month relapse rates were similar for both regimens. • Both levofloxacin and ciprofloxacin were well tolerated, with similar rates of adverse events.

Additional Evidence
Dose Simplification:
The quinolones are dosed either QD or BID. A literature search of Medline and Ovid did not reveal data on adherence and improved outcomes with quinolones.

Stable Therapy: Antibiotics, including quinolones may be changed due to treatment failure or resistance, however, no studies have evaluated the effect of changing quinolones during the same treatment course. A literature search of Medline and Ovid did not reveal data on the impact of changing antibiotic regimens.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical literature pertinent to use of the quinolones and physician visits.

IX. Conclusions

Fluoroquinolones are effective in the treatment of infections due to aerobic gram-negative and gram-positive (e.g., levofloxacin and sparfloxacin) bacteria. With the exception of sparfloxacin, most anaerobic bacteria are not susceptible to fluoroquinolones. However, phototoxicity is more common with sparfloxacin and lomefloxacin than with other fluoroquinolones; gemifloxacin has the lowest incidence of photosensitivity reactions in the class. Ciprofloxacin, gatifloxacin, levofloxacin and ofloxacin are very efficacious and have wide spectrum of activity with fewer side effects such as prolongation of the QT_c interval and phototoxicity when compared with other members of the class. Ciprofloxacin and ofloxacin are the agents available in generic formulations.

For uncomplicated UTI's, the quinolones have similar efficacies, but when pseudomonas is suspected or confirmed, ciprofloxacin is preferred. Generally ciprofloxacin has more FDA approved and treatment guideline recommended indications, minimal side effects, and overall safety and efficacy compared to other quinolones. Ciprofloxacin is also the only quinolone FDA approved for treatment of some pediatric infections (inhalational anthrax) and bone and joint infections. However, Cipro XR is only indicated for complicated and uncomplicated UTI and acute uncomplicated pyelonephritis. Overall, lomefloxacin has more limited coverage than the other quinolones with a significantly greater incidence of phototoxicity compared to the other drugs in the class. In prostatitis, ofloxacin is the drug of choice when *C. trachomatis* is suspected or confirmed.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand quinolone is recommended for preferred status.

Appendix A

Dosing for Ciprofloxacin

Ciprofloxacin Dosage Guidelines[4]					
Location of infection	Type or severity	Unit dose	Frequency	Daily dose	Usual durations[1]
Urinary tract	acute uncomplicated	100 or 250mg (500mg XR)	Q 12 h (q 24 h XR)	200 or 500mg (500mg XR)	3 days
	mild/moderate	250mg (200mg IV)	Q 12 h	500mg (400mg IV)	7 to 14 days
	severe/complicated[2]	500mg (400mg IV) (1000mg XR)	Q 12 h	1000mg (800mg IV) (1000mg XR)	7 to 14 days
Pyelonephritis	acute uncomplicated	1000mg XR	Q 24 h	1000mg XR	7 to 14 days
Lower respiratory tract Bone and joint Skin and skin structure	mild/moderate	500mg (400mg IV)	Q 12 h	1000mg (800mg IV)	7 to 14 days 4 to 6 weeks (bone and joint only)
	severe/complicated	750mg (400mg IV)	Q 12 h (q 8 h)	1500mg (1200mg)	7 to 14 days 4 to 6 weeks (bone and joint only)
Nosocomial pneumonia	mild/moderate/severe	400mg IV	Q 8 h	1200mg IV	10 to 14 days
Intra-abdominal[3]	Complicated	500mg (400 mg IV)	Q 12 h	1000mg (800mg IV)	7 to 14 days
Acute sinusitis	mild/moderate	500mg (400mg IV)	Q 12 h	1000mg (800mg IV)	10 days
Chronic bacterial prostatitis	mild/moderate	500mg (400mg IV)	Q 12 h	1000mg (800mg IV)	28 days
Empirical therapy in febrile neutropenic patients	severe: ciprofloxacin +piperacillin	400mg IV 50mg/kg IV	q 8 h q 4 h	1200mg IV not to exceed 24 g/day	7 to 14 days
Infectious diarrhea	mild/moderate/severe	500mg	Q 12 h	1000mg	5 to 7 days
Typhoid fever	mild/moderate	500mg	Q 12 h	1000mg	10 days
Urethral/Cervical gonococcal infections	uncomplicated	250mg	single dose	250mg	single dose
Inhalational anthrax (postexposure)[4]	adult	500mg (400mg IV)	Q 12 h	1000 mg (800 mg IV)	60 days
	pediatric	15mg/kg/dose, not to exceed 500mg/dose (10mg/kg/IV dose, not to exceed 400mg/IV dose)	Q 12 h	not to exceed 1000mg (not to exceed 800mg IV)	60 days

[1]Generally continue ciprofloxacin for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax(postexposure).
[2]Including secondary bacteremia from *E. coli* (IV only).
[3]Used in conjunction with metronidazole.
[4] Begin drug administration as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit. Total duration of ciprofloxacin administration(IV, IR, and suspension) for inhalational anthrax (postexposure) is 60 days.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Sulfonamides
Single Entity and Combination Agents
AHFS 081220
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I. Overview

The sulfonamide drug class consists of two distinct categories that will be reviewed. They are as follows:

- Single entity sulfonamides used to treat various infections (sulfadiazine and sulfisoxazole) as well as non-infectious conditions such as ulcerative colitis and rheumatoid arthritis.
- Combination products used for infectious diseases (sulfamethoxazole/trimethoprim and triple sulfa vaginal cream).

Specific indications for each anti-infective will be listed in the following sections, but as with all antibiotics, the only way to assure efficacy is by obtaining a culture and sensitivity. Even though some of these medications have specific indications and are preferred therapy for particular diseases, the most effective drug can change with resistant strains of bacteria that are emerging daily.

All of the drugs in this review have proven efficacy and safety profiles for particular disease states as will be highlighted in the following sections.

II. Evidence Based Medicine and Current Treatment Guidelines

Sulfonamides have been the standard of therapy for urinary tract infections for years. Many studies and reviews have verified the effectiveness and safety of these drugs. One review looked at 12 clinical trials and found that trimethoprim/sulfamethoxazole had a cure rate of 90% in children with single-dose therapy.[8] Yet another source recommends three-day therapy, but still touts sulfa preparations as a top choice for simple UTIs.[9] Two more references recommend the use of well-established antibiotics (which include sulfonamides) as first-line therapy unless contraindicated or if resistant strains are being treated.[10, 11] The consensus is to use these products whenever possible to treat UTIs because of their overall efficacy and safety.

A variety of other infectious diseases are also treated with sulfonamides. The CDC has recommendations for certain conditions such as toxoplasmosis and sexually transmitted diseases but most dosing information is available in package inserts.[3-7,29] Empiric dosing for certain FDA approved indications is often the standard of care, however, when in doubt, a culture and sensitivity would be the most reliable tool to assess effectiveness of a particular drug for a specific condition.

Sulfasalazine is currently indicated for use in ulcerative colitis and rheumatoid arthritis (RA) (only enteric coated). In studies, this drug has been found to be efficacious, providing substantial relief of symptoms and some decrease of X-ray progression. However, its use is hampered by the frequent occurrence of adverse events and the inability to maintain the benefits for a prolonged period of time.[23, 27] It does however, contribute to an improved long-term radiologic outcome in patients with early RA when used in triple therapy with combinations of DMARDs (disease-modifying antirheumatic drugs) or when added to another DMARD.[25,28]

Ulcerative colitis has also been the subject of studies comparing sulfasalazine to other medications. When compared to azathioprine, the relapse rates of colitis were comparable and trended towards earlier treatment failure with azathioprine.[13] When compared in efficacy to the 5-ASA medications in six trials, sulfasalazine was shown to be superior.[15] Even though

sulfasalazine is efficacious, adverse events can be more prevalent than with some of the other 5-ASA medications.[17,20] This fact did not prohibit its use, but some patients found it necessary to change medications because of the adverse events.

III. Comparative Indications for the Sulfonamide Single Entity Agents

Table 1 lists the agents included in this review. This review encompasses all dosage forms and strengths.

Table 1. Sulfonamide Single Entity Agents In This Review

Generic Name	Formulation	Example Brand Name (s)
Sulfadiazine	Oral	Generic only available
Sulfasalazine	Oral	*Azulfidine, Azulfidine EN, *Sulfazine
Sulfisoxazole	Oral	Gantrisin Pediatric Suspension *Gantrisin tablets

*Generic Available

Table 2. FDA-Approved Indications for Sulfonamide Single Entity Agents [1-6]

Indictions	Sulfadiazine	Sulfasalazine	Sulfisoxazole
Chancroid	√		√
Inclusion conjunctivitis	√		√
Malaria [1]	√		√
Meningitis, *Haemophilus influenzae*	√		√
Meningococcal [2]	√		√
Nocardiosis	√		√
Otitis media, acute [3]	√		√
Rheumatic fever	√		
Toxoplasmosis [4]	√		√
Trachoma	√		√
Urinary tract infections [5] (pyelonephritis, cystitis)	√		√
Ulcerative Colitis		√ (Azulfidine and Azulfidine EN)	
Rheumatoid Arthritis [6] (RA)		√ (Azulfidine EN only)	
Juvenile Rheumatoid Arthritis [7] (JRA)		√ (Azulfidine EN only)	

[1] As adjunctive therapy because of chloroquine-resistant strains of *Plasmodium falciparum*.
[2] When the organism is susceptible and for prophylaxis when sulfonamide-sensitive group A strains prevail.
[3] Caused by *H. influenzae* when used with penicillin.
[4] As adjunctive therapy with pyrimethamine.
[5] In the absence of obstructive uropathy or foreign bodies when caused by *Escherichia coli, Klebsiella-Enterobacter, Staphylococcus aureus, Proteus mirabilis, and P. vulgaris*.
[6] In the treatment of patients with RA who have responded inadequately to saliclyates or other nonsteroidal anti-inflammatory drugs.
[7] In the treatment of pediatric patients ≥ 6 years of age with polyarticular-course JRA who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs.

IV. Pharmacokinetic Parameters of the Sulfonamide Single Entity Agents[3,5,6]

Mechanism of action
Sulfonamides exert their bacteriostatic action by competitive antagonism of para-aminobenzoic acid (PABA), an essential component in folic acid synthesis. Microorganisms that require exogenous folic acid and do not synthesize folic acid are not susceptible to the action of sulfonamides.

Absorption and Distribution
The oral sulfonamides are readily absorbed from the GI tract. Approximately 70% to 100% of an oral dose is absorbed. These agents are distributed throughout all body tissues and readily enter the cerebrospinal fluid, pleura, synovial fluids, the eye, the placenta, and the fetus. Sulfonamides are bound to plasma proteins in varying degrees. "Free" sulfonamide serum levels of 5 to 15mg/dL may be therapeutically effective for most infections; avoid levels > 20mg/dL.

Specifically, the absolute bioavailability of sulfasalazine is < 15% for the parent drug. Detectable serum concentrations of sulfasalazine have been found in healthy subjects within 90 minutes after the dose. Sulfasalazine is highly bount to albumin (> 99.3%).

Metabolism and Excretion
Metabolism occurs in the liver by conjugation and acetylation to inactive metabolites. Individuals who are slow acetylators have an increased risk of toxicity from sulfonamide accumulation.

Renal excretion is mainly by glomerular filtration. Some of the acetylated metabolites are less soluble and may contribute to crystalluria and renal complications. To prevent the possibility of crystalluria, alkalinization of the urine and adequate fluid intake are recommended when using the less soluble sulfonamides (e.g., sulfadiazine). Small amounts are eliminated in the feces, bile, breast milk, and other secretions.

In the intestine, sulfasalazine is metabolized by intestinal bacteria to SP and 5-ASA. OF the two metabolites, SP is well absorbed from the colon (estimated bioavailability of 60%) and highly metabolized. 5-ASA is absorbed less than SP with an estimated bioavailability of 10% to 30%. The half-life of sulfasalazine is 7.6 hours and renal clearance is estimated to account for 37% of total clearance. Absorbed SP and 5-ASA is primarily eliminated in the urine either as free metabolites or as glucuronide conjugates. The majotiry of 5-ASA stays within the colon and is excreted as 5-ASA and acetyl-5-ASA in the feces.

Elderly
Elderly patients with rheumatoid arthritis show a prolonged plasma half-life for sulfasalazine, SP, and the metabolites.

Fast/Slow Acetylators
The metabolism of SP to AcSp is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the white population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life for SP (14.8 vs. 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. Patients who are slow acetylators of SP show a higher incidence of adverse events.

V. Drug Interactions of the Sulfonamide Single Entity Agents

Table 3. Documented Drug Interactions for Sulfonamide Single Entity Agents [1, 2, 3,5,6]

Precipitant Drug	Object Drug*		Description
Sulfonamides	Anticoagulants, oral	↑	Warfarin's anticoagulation action may be enhanced. Hemorrhage could occur.
Sulfonamides	Cyclosporine	↓	Cyclosporine concentrations are decreased, and the risk of nephrotoxicity may be increased.
Sulfonamides	Hydantoins	↑	Serum hydantoin levels may be increased.
Sulfonamides	Methotrexate	↑	The risk of methotrexate-induced bone marrow suppression may be enhanced.
Sulfonamides	Sulfonylureas	↑	Increased sulfonylurea half-lives and hypoglycemia may occur.
Sulfonamides	Tolbutamide	↑	The half-life of tolbutamide may be prolonged when administered with sulfamethizole.
Sulfonamides	Uricosuric agents	↑	Potentiation of uricosuric action may be noted.
Diuretics (e.g., thiazide)	Sulfonamides	↑	Coadministration may cause an increased incidence of thrombocytopenia with purpura.
Indomethacin	Sulfonamides	↑	Sulfonamides may be displaced fromplasma albumin resulting in increased free-drug concentrations.
Methenamine	Sulfonamides	↑	An insoluble precipitate may form in acidic urine when sulfamethizole is used concomitantly with methenamine mandelate.
Probenecid	Sulfonamides	↑	Sulfonamides may be displaced from plasma albumin resulting in increased free-drug concentrations.
Salicylates	Sulfonamides	↑	Sulfonamides may be displaced from plasma albumin resulting in increased free-drug concentrations.
Sulfasalazine	Digoxin	↓	Reduced absorption of digoxin has been reported when coadministered with sulfasalazine.
Sulfasalazine	Folic Acid	↓	Reduced GI absorption of folic acid has been reported when coadministered with sulfasalazine. Periodically monitor patients taking sulfasalazine. If folate deficiency is noted, potential treatment measures include increasing dietary folate, giving sulfasalazine between meals, and administering additional folic acid or folinic acid.

* ↑ = Object drug increased. ↓ = Object drug decreased.

VI. Adverse Drug Events

Sulfonamides

Table 4a. Adverse Events Reported for the Sulfonamide Single Entity [Agents 1,2, 3,5,6]

System Affected	Adverse Event
CNS	Headache; peripheral neuropathy; mental depression; convulsions; ataxia; hallucinations; tinnitus; vertigo; insomnia; apathy; drowsiness; polyneuritis neuritis; optic neuritis; transient myopia.
GI	Nausea; emesis; abdominal pains; diarrhea; anorexia; pancreatitis; stomatitis; hepatitis; hepatocellular necrosis; pseudomembranous enterocolitis; glossitis.
Hematologic	Agranulocytosis; aplastic anemia; thrombocytopenia; leukopenia; hemolytic anemia; purpura; hypoprothrombinemia; neutropenia; eosinophilia; methemoglobinemia.
Hypersensitivity	Stevens-Johnson type erythema multiforme; generalized skin eruptions; allergic myocarditis; epidermal necrolysis; urticaria; periarteritis nodosum; serum sickness; pruritus; exfoliative dermatitis; anaphylactoid reactions; periorbital edema; conjunctival, scleral injection; photosensitization; arthralgia; allergic myocarditis; transient pulmonary changes with eosinophilia and decreased pulmonary function.
Renal	Crystalluria; elevated creatinine; toxic nephrosis with oliguria and anuria.
Miscellaneous	Drug fever; chills; pyrexia; L.E. phenomenon. Reports of adverse effects in breastfeeding infants are rare.
Other	The sulfonamides bear chemical similarities to some goitrogens, diuretics (acetazolamide and thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

Sulfasalazine: Ulcerative Colitis and Rheumatoid Arthritis

The most common adverse reactions associated with sulfasalazine in ulcerative colitis are anorexia, headache, nausea, vomiting, gastric distress, and reversible oligospermia. These occur in approximately 33% of patients. Less frequent adverse reactions are skin rash, pruritus, urticaria, fever, Heinz body anemia, hemolytic anemia, and cyanosis, which may occur at a frequency of = 1 in 30 patients.[5]

Similar adverse reactions are associated with use in adult RA, although there was a greater incidence of some reactions. In RA studies, the following common adverse reactions were noted: Nausea (19%); dyspepsia, rash (13%); headache (9%); abdominal pain, vomiting (8%); fever (5%); dizziness, stomatitis, pruritus, abnormal liver function tests (4%); leukopenia (3%); thrombocytopenia (1%). One report showed a 10% rate of immunoglobulin suppression, which was slowly reversible and rarely accompanied by clinical findings.[5]

The following adverse reactions in Table 4b occur rarely (approximately ≤ 1in 1000 patients).

Table 4b. Adverse Reactions Reported for Sulfasalazine[1,2,5,6]

System Affected	Adverse Event
CNS	Transverse myelitis; convulsions; meningitis; transient lesions of the posterior spinal column; cauda equina syndrome; Guillain-Barré syndrome; peripheral neuropathy; mental depression; vertigo; hearing loss; insomnia; ataxia; hallucinations; tinnitus; drowsiness.
GI	Hepatitis; pancreatitis; bloody diarrhea; impaired folic acid absorption; impaired digoxin absorption; stomatitis; diarrhea; abdominal pains; neutropenic enterocolitis.
Hematologic	Aplastic anemia; agranulocytosis; leukopenia; megaloblastic (macrocytic) anemia; purpura; thrombocytopenia; hypoprothrombinemia; methemoglobinemia; congenital neutropenia; myelodysplastic syndrome.
Hypersensitivity	Erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; epidermal necrolysis (Lyell's syndrome) with corneal damage; anaphylaxis; serum sickness syndrome; pneumonitis with or without eosinophilia; vasculitis; fibrosing alveolitis; pleuritis; pericarditis with or without tamponade; allergic myocarditis; polyarteritis nodosa; lupus erythematosus-like syndrome; hepatitis and hepatic necrosis with or without immune complexes; fulminant hepatitis, sometimes leading to liver transplantation; parapsoriasis varioformis acuta (Mucha-Haberman syndrome); rhabdomyolysis; photosensitization; arthralgia; periorbital edema; conjunctival and scleral injection; alopecia.
Renal	Toxic nephrosis with oliguria and anuria; nephritis; nephrotic syndrome; hematuria; crystalluria; proteinuria; hemolytic-uremic syndrome.
Miscellaneous	Urine discoloration; skin discoloration.
Other	***Children:*** In general, the adverse reactions in JRA patients are similar to those seen in patients with adult RA except for a high frequency of serum sickness-like syndrome in systemic-course JRA.

VII. Dosing and Administration for the Sulfonamide Single Entity Agents

Table 5. Dosing for the Sulfonamide Single Entity Agents for Infectious Diseases[1,2,3,5,6]

	Availability	Dose /Frequency/Duration
Sulfadiazine	500mg oral tablets	**Adults:** Loading dose: 2 to 4g. Maintenance dose: 2 to 4g/day in 3 to 6 divided doses. **Children (> 2 months):** Loading dose: 75mg/kg (or 2g/m^2). **Maintenance dose:** 150mg/kg/day (4g/m^2/day) in 4 to 6 divided doses. **Maximum dose:** 6g/day Contraindicated in infants < 2 months old (except in congenital toxoplasmosis as an adjunct with pyrimethamine). Other recommended doses for toxoplasmosis (for 3 to 4 weeks) include: Infants (< 2 months): 25mg/kg/dose 4 times daily. Children (> 2 months): 25 to 50mg/kg/dose 4 times daily. Prevention of recurrent attacks of rheumatic fever: Patients > 30kg (> 66lbs) - 1g/day; <30kg (< 66lbs) - 0.5g/day.

<table>
<tr>
<td>Sulfasalazine</td>
<td>500mg oral tablets</td>
<td>
Ulcerative colitis:
Initial therapy:
Adults: 3 to 4g daily in evenly divided doses. It may be advisable to initiate therapy with a lower dosage (e.g., 1 to 2g daily), to reduce possible GI intolerance.

Children [3] 2 years of age: 40 to 60mg/kg body weight in each 24-hour period, divided into 3 to 6 doses.

Maintenance therapy:
Adults: 2g daily.

Children [3] 2 years of age: 30mg/kg body weight in each 24-hour period, divided into four doses.

It is often necessary to continue medication even when clinical symptoms, including diarrhea, have been controlled. When endoscopic examination confirms satisfactory improvement, reduce dosage to a maintenance level. If diarrhea recurs, increase dosage to previously effective levels.
</td>
</tr>
<tr>
<td></td>
<td>500mg oral tablets, enteric coated, delayed-release</td>
<td>
Adult RA: 2g daily in two evenly divided doses. It is advisable to initiate therapy with a lower dosage (e.g., 0.5 to 1g daily) to reduce possible GI intolerance. A suggested dosing schedule is given below.

In RA, the effect of sulfasalazine delayed-release tablets can be assessed by the degree of improvement in the number and extent of actively inflamed joints.

<table>
<tr><th colspan="3">Adult RA Sulfasalazine Dosing Schedule</th></tr>
<tr><th rowspan="2">Week of treatment</th><th colspan="2">Number of delayed-release tablets</th></tr>
<tr><th>Morning</th><th>Evening</th></tr>
<tr><td>1</td><td>--</td><td>1</td></tr>
<tr><td>2</td><td>1</td><td>1</td></tr>
<tr><td>3</td><td>1</td><td>2</td></tr>
<tr><td>4</td><td>2</td><td>2</td></tr>
</table>
A therapeutic response has been observed as early as four weeks after starting treatment, but treatment for 12 weeks may be required in some patients before clinical benefit is noted. Give consideration to increasing the daily dose to 3g if the clinical response after 12 weeks is inadequate. Careful monitoring is recommended for doses > 2g/day.

JRA-polyarticular course:
Children [3] 6 years of age: 30 to 50mg/kg of body weight daily in two evenly divided doses. Typically, the maximum dose is 2g/day. To reduce possible GI intolerance, begin with a quarter to a third of the planned maintenance dose and increase weekly until reaching the maintenance dose at one month.
</td>
</tr>
</table>

		Desensitization: Some patients may be sensitive to treatment. These regimens suggest starting with a total daily dose of 50 to 250mg initially, and doubling it every four to seven days until the desired therapeutic level is achieved. Discontinue if the symptoms of sensitivity recur. Do not attempt desensitization in patients who have a history of agranulocytosis or who have experienced an anaphylactoid reaction while previously receiving sulfasalazine. **Ulcerative colitis:** ***Initial therapy:*** **Adults:** 3 to 4g daily in evenly divided doses. It may be advisable to initiate therapy with a lower dosage (e.g., 1 to 2g daily), to reduce possible GI intolerance. **Children ³ 2 years of age:** 40 to 60mg/kg body weight in each 24-hour period, divided into three to six doses. ***Maintenance therapy:*** **Adults:** 2g daily. **Children ³ 2 years of age:** 30mg/kg body weight in each 24-hour period, divided into four doses. It is often necessary to continue medication even when clinical symptoms, including diarrhea, have been controlled. When endoscopic examination confirms satisfactory improvement, reduce dosage to a maintenance level. If diarrhea recurs, increase dosage to previously effective levels.
Sulfisoxazole	500mg or tablets 500mg/5ml suspension	**Loading dose: 2 to 4g.** **Maintenance dose:** 4 to 8g/day in 4 to 6 divided doses. **Children and infants (> 2 months):** Initial dose: 75mg/kg. Maintenance dose: 150mg/kg/day (4g/m^2/day) in 4 to 6 divided doses (max, 6g/day). CDC recommended treatment schedules for sexually transmitted diseases ((Morbidity and Mortality Weekly Report 1993 Sep 24;42 (No. RR-14):i-102.)): Lymphogranuloma venereum: As an alternative regimen to doxycycline, sulfisoxazole 500mg 4 times/day for 21 days or equivalent sulfonamide course. **Chlamydia trachomatis infections:** As an alternative regimen to doxycycline or azithromycin (or if erythromycin is not tolerated), sulfisoxazole 500mg four times/day for 10 days or equivalent sulfonamide course. Contraindicated in infants < 2 months old (except in congenital toxoplasmosis as an adjunct with pyrimethamine).

Contraindications:
Hypersensitivity to sulfonamides or chemically related drugs (e.g., sulfonylureas, thiazide and loop diuretics, carbonic anhydrase inhibitors, sunscreens with PABA, local anesthetics); pregnancy at term, lactation (see Warnings); infants < 2 months of age (except in congenital toxoplasmosis as adjunct with pyrimethamine).

Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sore throat, fever, pallor, purpura, or jaundice may be early indications of serious blood disorders. Perform complete blood counts.

Group A beta-hemolytic streptococcal infections:
Do not use for treatment of these infections. In an established infection, they will not eradicate the streptococcus and will not prevent sequelae, such as rheumatic fever and glomerulonephritis.

Hypersensitivity reactions:
May cause cholestatic jaundice.

Renal function impairment:
Use with caution. The frequency of renal complications is considerably lower in patients receiving the more soluble sulfonamides (sulfisoxazole). Maintain adequate fluid intake (2 to 3L/day) to prevent crystalluria and stone formation.

Hepatic function impairment:
Cholestatic jaundice occurs in 0.5% to 1% of patients because of hypersensitivity or idiosyncrasy.

Pregnancy:
Category C. Safety for use during pregnancy is not established. Sulfonamides cross the placenta; fetal levels average 70% to 90% of maternal serum levels. Significant levels may persist in the neonate if these drugs are given near term; jaundice, hemolytic anemia and kernicterus may occur. Teratogenicity (e.g., tracheoesophageal fistula, cataracts) has occurred in some animal species. Do not use at term.

Lactation:
Sulfonamides are excreted in breast milk in low concentrations. According to the American Academy of Pediatrics, breastfeeding and sulfonamide use are compatible because sulfonamide excretion into breast milk does not pose a significant risk to the healthy full-term neonate. However, do not nurse premature infants or those with hyperbilirubinemia or G-6-PD deficiency.

Children:
Do not use in infants < 2 months of age (except for congenital toxoplasmosis as adjunctive therapy with pyrimethamine).

Monitoring:
Monitor blood counts frequently, especially during prolonged administration. Perform microscopic urinalyses once a week when a patient is treated for > 2 weeks. Use urine cultures to confirm eradication of bacteriuria.

Allergy or asthma:
Give with caution to patients with severe allergy or bronchial asthma.

Hemolytic anemia:
Frequently dose-related, this may occur in G-6-PD deficient individuals.

Photosensitivity:
Photosensitization (photoallergy or phototoxicity) may occur; therefore, caution patients to take protective measures (e.g., sunscreens, protective clothing) against exposure to ultraviolet light or sunlight until tolerance is determined.

VIII. Comparative Effectiveness of the Sulfonamide Single Entity Agents

Limited comparative studies are available for the single entity sulfonamides for infectious diseases.

Table 6. Additional Outcomes Evidence for the Sulfonamide Single Entity Agents

Study	Sample	Design	Results
Jordon MK, et al.[30]	n=8	2000mg Sulfadiazine BID vs. 1000mg QID for suppression of toxoplasmosis	• No differences in pharmacokinetic parameters were detected between the regimens. Conclusion: Data provides a pharmacokinetic rationale for BID dosing of Sulfadiazine for the treatment and suppression of toxoplasmosis.
CDC MMWR[29]	N/A	Preventing Congenital Toxoplasmosis	• Treatment of toxoplasmosis in immunocompetent persons usually consists of pyrimethamine and sulfadiazine • Treatment in pregnant women consists of spiramycin with/without sulfadiazine or pyrimethamine and sulfadiazine.
Sood A, et al.[13]	n=25	18 months	• In this prospective, randomized, open-label study, 25 patients with severe ulcerative colitis received either azathioprine (2.5mg/Kg/day; Group A, n = 12) or sulfasalazine (6g/day; Group B, n = 13). All patients received oral corticosteroids in a tapering dosage schedule initially. Treatment failure was defined as either disease relapse or drug withdrawal because of adverse effects. • Five of 12 patients in Group A and 8 of 13 patients in Group B had sustained remission during the stipulated study period of 18 months (p = ns). Two patients in Group A had to stop azathioprine because of adverse effects (bone marrow suppression and acute pancreatitis). In Group A, all patients who had treatment failure developed it in the first half of the study while in Group B treatment failure occurred in both halves. CONCLUSIONS: The relapse rate of ulcerative colitis on maintenance therapy with azathioprine or sulfasalazine is comparable; there was a trend towards earlier treatment failure with azathioprine.
Loftus EV, et al.[17]	46 trials	Various	• A review to determine whether there is a difference in short-term adverse events in patients with ulcerative colitis treated with mesalazine, olsalazine or balsalazide. • MEDLINE was searched for articles published until 2002. Randomized trials of oral mesalazine, olsalazine or balsalazide for the treatment of active disease or the maintenance of remission were included. • Outcomes of interest were the frequencies of patients experiencing adverse events and those withdrawn due to adverse events. • Forty-six trials were included. One study of mesalazine vs. sulfasalazine for active colitis showed significantly fewer patients with adverse events with mesalazine. Both balsalazide vs. sulfasalazine studies for active disease showed significantly fewer withdrawals with balsalazide. One trial of balsalazide vs. sulfasalazine for maintenance showed significantly fewer patients with adverse events with balsalazide. Otherwise, no significant differences in safety outcomes were noted. CONCLUSION: All three 5-aminosalicylic acid agents are safe in the short term. In mesalazine-treated patients, the frequencies of adverse events or withdrawals due to adverse events were comparable with those in placebo-treated patients and lower than those in sulfasalazine-treated patients. Overall, adverse events or withdrawals were not significantly more frequent with olsalazine than with placebo or sulfasalazine. Adverse events and study withdrawals on balsalazide were less frequent than those on sulfasalazine.

Korpela M, et al.[25]	n=195	5 years	• This study was to evaluate the long-term frequency of disease remissions and the progression of joint damage in patients with early rheumatoid arthritis (RA) who were initially randomized to two years of treatment with either a combination of three disease-modifying antirheumatic drugs (DMARDs) or a single DMARD. • Patients with early, clinically active RA were randomly assigned to treatment with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone or with a single DMARD (initially, sulfasalazine) with or without prednisolone. • After two years, the DMARD and prednisolone treatments became unrestricted, but were still targeted toward remission. • The long-term effectiveness was asses sed by recording the frequency of remissions and the extent of joint damage seen on radiographs of the hands and feet obtained annually up to five years. Radiographs were assessed by the Larsen score. • A total of 160 patients (78 in the combination group and 82 in the single group) completed the five-year extension study. At two years, 40% of the patients in the combination-DMARD group and 18% in the single-DMARD group had achieved remission (P < 0.009). At five years, the corresponding percentages were 28% and 22% (P not significant). The median Larsen radiologic damage scores at baseline, two years, and five years in the combination-DMARD and single-DMARD groups were zero and two (P = 0.50), four and 12 (P = 0.005), and 11 and 24 (P = 0.001), respectively. CONCLUSION: Aggressive initial treatment of early RA with the combination of three DMARDs for the first two years limits the peripheral joint damage for at least five years. Our results confirm the earlier concept that triple therapy with combinations of DMARDs contributes to an improved long-term radiologic outcome in patients with early and clinically active RA.
Dougados M, et al.[28]	n=106	24 weeks	• Patients with active RA (Disease Activity Score 28 [DAS 28] >3.2) enrolled in the first open-label phase of the RELIEF study received leflunomide for 24 weeks. Inadequate responders then entered the double-blind phase and received a further 24 weeks' treatment with leflunomide (20mg once-daily [QD]) plus sulfasalazine (final dose 2g QD), or placebo plus sulfasalazine (dose as above). • A total of 106 inadequate responders entered the double-blind phase; 56 received leflunomide plus sulfasalazine, and 50 received placebo plus sulfasalazine. In the intent-to-treat population, more patients receiving leflunomide plus sulfasalazine (44.6%) achieved a DAS 28 response at endpoint versus those receiving placebo plus sulfasalazine (34.0%) (p=0.179). • In the week 24 completers, more patients receiving leflunomide plus sulfasalazine (30.4%) were DAS 28 responders versus those receiving placebo plus sulfasalazine (20.0%) (p=0.081). • Comparable numbers of patients in each treatment group were ACR 20% responders; however, the ACR 50% response rate was significantly higher in the leflunomide plus sulfasalazine group (8.9%) versus the placebo plus sulfasalazine group (0%) (p=0.038). The safety profiles of both treatment groups were comparable. CONCLUSION: Although small patient numbers do not allow firm conclusions, these results indicate a favorable, but not statistically significant benefit for combining leflunomide with sulfasalazine over switching to sulfasalazine alone in RA patients inadequately responding to leflunomide.

Additional Evidence

Dose Simplification: This is not an issue with sulfadiazine or sulfisoxazole since no special release formulations are available. However, with the sulfasalazine enteric coated tablets, less frequent dosing is available compared to that with immediate release dosing (QID to BID dosing). A literature search of Medline and Ovid did not reveal evidence to support a clinical advantage of the enteric coated tablets over the immediate release formulation.

Stable Therapy: Some studies did change medications because of side effects and/or efficacy with no adverse consequences. No data was found in Medline or Ovid on changing from sulfasalazine therapy in rheumatoid arthritis or ulcerative colitis to other treatments; however, other therapies are available.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical literature relevant to use of the sulfonamides, including sulfasalazine, and any impact on physician visits.

IX. Conclusions

The sulfonamide products are available generically, with the exception of Azulfidine EN tablets and Gantrisin Pediatric suspension. Gantrisin Pediatric suspension is a branded product and although it has its place in therapy for use in children, it is comparable in efficacy with the generic tablet formulation. The suspension offers an alternative treatment option for children unable to take the oral tablets. Sulfasalazine is an option for patients with rheumatoid arthritis and ulcerative colitis, but is not typically a first-line agent for either condition. Sulfasalazine is used in patients who have not adequately responded to other therapies (e.g. NSAIDs in RA or JRA). The immediate-release tablets are available as a generic formulation. Although only the enteric coated sulfasalazine product (Azulfidine EN) is indicated in the treatment of RA and JRA, other recommended treatments for both conditions are available and are clinically effective.

Therefore, all brand products within this class are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over alternatives in general use.

X. Recommendations

No brand single entity sulfonamide agent is recommended for preferred status.

Combination Sulfonamides

I. Comparative Indications of the Combination Sulfonamides

This review encompasses all dosage forms and strengths.

Table 1. Combination Sulfonamide Products in this Review

Generic Name	Formulation	Example Brand Names (s)
Trimethoprim and Sulfamethoxazole (TMP-SMZ)	Oral tablets	*Bactrim, Septra, Bethaprim SS
Trimethoprim and Sulfamethoxazole DS	Oral tablets	*Bactrim DS, Septra DS, Bethaprim DS
Trimethoprim and Sulfamethoxazole	Oral suspension	*Cotrim Pediatric, Septra, Sulfatrim
Trimethoprim and Sulfamethoxazole	Injection	*Bactrim IV, Septra IV
Triple Sulfa (sulfathiazole, sulfacetamide, sulfabenzamide)	Vaginal cream and tablets	Gyne-Sulf,Trysul,Vagilia, V.V.S., Sultrin, Dayto-Sulf, Triple Sulfa Vaginal

*Generic available.

Table 2. FDA-Approved Indications for the Combination Sulfonamides

Product	Indication
Trimethoprim and Sulfamethoxazole (all formulations)[4-7]	**Oral and parenteral:** *Urinary tract infections (UTIs) due to susceptible strains of E. coli, Klebsiella and Enterobacter species, M. morganii, P. mirabilis and P. vulgaris:* • Treat initial uncomplicated UTIs with a single antibacterial agent. • Parenteral therapy is indicated in severe or complicated infections when oral therapy is not feasible. ***Shigellosis enteritis:*** Caused by susceptible strains of *S. flexneri* and *S. sonnei* in children and adults. ***Pneumocystis carinii pneumonia (PCP):*** Treatment of PCP in children and adults. **Oral:** ***Pneumocystis carinii pneumonia:*** Prophylaxis against PCP in individuals who are immunosuppressed and considered to be at increased risk. ***Acute otitis media in children:*** Due to susceptible strains of *H. influenzae* or *S. pneumoniae*. There are limited data on the safety of repeated use in children < 2 years of age. Not indicated for prophylactic use or prolonged administration. ***Acute exacerbations of chronic bronchitis in adults:*** Due to susceptible strains of *H. influenzae* and *S. pneumoniae*. ***Travelers' diarrhea in adults:*** Due to susceptible strains of enterotoxigenic *E. coli*.
Triple sulfa vaginal[35-41]	**Original indication:** Vaginitis caused by *Haemophilus (Gardnerella) vaginalis*-see FDA announcement and current opinion below. **Unaccepted**[35] The U.S. Food and Drug Administration (FDA) announced on May 31, 1979, that its Anti-infective and Topical Drugs Advisory Committee and Fertility and Maternal Health Advisory Committee, as well as other studies, had concluded there was no adequate evidence that the then-available vaginal sulfonamides formulations were

	effective either for the treatment of vulvovaginitis caused by *Candida albicans*, *Trichomonas vaginalis*, or *Gardnerella vaginalis (Haemophilus vaginalis)* or for relief of the symptoms of these conditions. In addition, in the opinion of USP medical experts, triple sulfa vaginal preparations are not effective for any indication, including vulvovaginitis caused by *Gardnerella vaginalis* and use as a deodorant in saprophytic infections following radiation therapy. Also, USP medical experts do not recommend the use of vaginal sulfonamides, including the reformulated single-entity preparations, for the treatment of fungal infections of the vagina.

II. Pharmacokinetic Parameters

Table 3. Pharmacokinetic Parameters of the Combination Sulfonamides[4-7]

Parameter	Explanation
Absorption/Distribution	TMP-SMZ is rapidly and completely absorbed following oral administration. Peak plasma levels occur in one to four hours following oral administration and 1 to 1.5 hours after IV infusion. The 1:5 ratio of TMP to SMZ achieves an approximate 1:20 ratio of peak serum concentrations. Detectable amounts of TMP-SMZ are present in the blood 24 hours after administration. During 3 days of administration of 160mg TMP/800mg SMZ twice daily, the mean steady-state plasma TMP concentration was 1.72mcg/ml. The steady-state mean plasma levels of free and total SMZ were 57.4mcg/ml and 68mcg/ml, respectively. Approximately 44% of TMP and 70% of SMZ are protein bound. Both distribute to sputum, vaginal fluid and middle ear fluid, pass the placental barrier, and are excreted in breast milk; TMP also distributes to bronchial secretion. Two to three times the serum concentration of TMP is achieved in prostatic fluid. Therapeutic concentrations are achieved in vaginal secretions, cerebrospinal fluid, pulmonary tissue, pleural effusion, bile, sputa and aqueous humor. It is also detectable in breast milk, amniotic fluid and fetal serum. Following oral administration, the half-lives of TMP (8 to 11 hours) and SMZ (10 to 12 hours) are similar. Following IV administration, the mean plasma half-life was 11.3 ± 0.7 hours for TMP and 12.8 ± 1.8 hours for SMZ. Patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment.
Metabolism/Excretion	TMP is metabolized to a relatively small extent; SMZ undergoes biotransformation to inactive compounds. The metabolism of SMZ occurs predominantly by N_4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of TMP are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free forms are the therapeutically active forms. Excretion is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations are considerably higher than serum concentrations. Concurrent administration does not affect the excretion pattern of either drug. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose is 84.5% for total sulfonamide and 66.8% for free TMP. Of the total sulfonamide, 30% is excreted as free SMZ, with the remaining as N_4-acetylated metabolite.

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III. Drug Interactions with Combination Sulfonamides

Table 4. Drug Interactions [4-7]

Precipitant drug	Object drug*		Description
TMP-SMZ	Anticoagulants	↑	The prothrombin time of warfarin may be prolonged. Monitor coagulation tests and adjust dosage as required.
TMP-SMZ	Cyclosporine	↓	A decrease in the therapeutic effect of cyclosporine and an increased risk of nephrotoxicity has occurred.
TMP-SMZ	Dapsone	↑	Increased serum levels of both dapsone and TMP may occur.
Dapsone	TMP-SMZ	↑	
TMP-SMZ	Diuretics	↑	In elderly patients, concomitant use has increased incidence of thrombocytopenia with purpura.
TMP-SMZ	Hydantoins	↑	Phenytoin's hepatic clearance may be decreased and the half-life prolonged.
TMP-SMZ	Methotrexate	↑	Sulfonamides can displace methotrexate (MTX) from plasma protein binding sites, thus increasing free MTX concentrations; bone marrow depressant effects may be potentiated.
TMP-SMZ	Sulfonylureas	↑	The hypoglycemic response may be increased.
TMP-SMZ	Zidovudine	↑	The serum levels of zidovudine may be increased due to a decreased renal clearance.

* ↑ = Object drug increased. ↓ = Object drug decreased.

IV. Adverse Drug Events of the Combination Sulfonamides

Most common:[5]
GI disturbances (nausea, vomiting, anorexia); allergic skin reactions (e.g., rash, urticaria).

Table 5. Other Adverse Drug Reactions [4-7]

System or Route Affected	Adverse Event
Parenteral therapy	**Parenteral therapy:** Local reaction, pain and slight irritation on IV administration (infrequent); thrombophlebitis (rare).
CNS	Headache; mental depression; convulsions; ataxia; hallucinations; tinnitus; vertigo; insomnia; apathy; fatigue; weakness; nervousness; aseptic meningitis; peripheral neuritis.
GI	Glossitis; anorexia; stomatitis; nausea; emesis; abdominal pain; diarrhea; pseudomembranous enterocolitis; hepatitis (including cholestatic jaundice and hepatic necrosis); pancreatitis; elevation of serum transaminase and bilirubin.
GU	Renal failure; interstitial nephritis; BUN and serum creatinine elevation; toxic nephrosis with oliguria and anuria; crystalluria.
Hematologic	Agranulocytosis; aplastic, hemolytic or megaloblastic anemia; thrombocytopenia; leukopenia; neutropenia; hypoprothrombinemia; eosinophilia; methemoglobinemia; hyperkalemia; hyponatremia.
Hypersensitivity	Erythema multiforme; Stevens-Johnson syndrome; generalized skin eruptions; rash; toxic epidermal necrolysis; urticaria; serum sickness-like syndrome; pruritus; exfoliative dermatitis; anaphylactoid reactions; conjunctival and scleral injection; photosensitization; allergic myocarditis; angioedema; drug fever; chills; Henoch-Schoenlein purpura; systemic lupus erythematosus; generalized allergic reactions; periarteritis nodosa.
Musculoskeletal	Arthralgia; myalgia.
Respiratory	Pulmonary infiltrates

V. Dosing and Administration for the Combination Sulfonamides

Table 6. Dosing and Administration for Sulfamethoxazole/Trimethoprim[4-7]

Organisms and/or Infections	Dosage	
Urinary tract infections, shigellosis and acute otitis media:	Adults: 160mg TMP/800mg SMZ every 12 hours for 10 to 14 days (5 days for shigellosis).	
	Children (= 2 months of age): 8mg/kg TMP/40mg/kg SMZ per day given in 2 divided doses every 12 hours for 10 days (5 days for shigellosis).	
Guideline for proper dosage:	**Dose every 12 hours:**	
Weight (kg) 10 20 30 40	Teaspoonfuls 1 (5ml) 2(10ml) 3 (15ml) 4 (20ml)	Tablets - 1 11/2 2 (or 1 double strength tablet)
Patients with impaired renal function Ccr (ml/min):	**Recommended dosage regimen:**	
> 30 15-30 <15	Usual regimen 1/2 usual regimen Not recommended	
Adults and children >2 months with normal renal function for severe UTIs and shigellosis.	8 to 10mg/kg/day(based on TMP) in 2 to 4 divided doses every 6, 8 or 12 hours for up to 14 days for severe UTIs and 5 days for shigellosis.	
Travelers' diarrhea in adults:	160mg TMP/800mg SMZ every 12 hrs for 5 days.	
Acute exacerbations of chronic bronchitis in adults:	160mg TMP/800mg SMZ every 12 hrs for 14 days.	
Pneumocystis carinii pneumonia:		
Treatment :	15 to 20mg/kg TMP/100mg/kg SMZ per day in divided doses every 6 hours for 14 to 21 days.	
Guideline for proper dosage in children	**Dose every 6 hours:**	
Weight (kg) 8 16 24 32	Teaspoonfuls 1 (5ml) 2(10ml) 3 (15ml) 4 (20ml)	Tablets - 1 11/2 2 (or 1 double strength tablet)
IV for adults and children > 2 months:	15 to 20mg/kg/day (based on TMP) in 3 or 4 divided doses every 6 to 8 hours for up to 14 days.	
Prophylaxis :		
Adults:	160mg TMP/800mg SMZ given orally every 24 hours.	
Children:	150mg/m^2 TMP/ 750mg/m^2 SMZ per day given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 320mg TMP/1600mg SMZ.	
Guideline for proper dosage in children	Dose every 12 hours	
Body surface area (m^2) 0.26 0.53 1.06	Teaspoonfuls 1/2 (2.5ml) 1 (5ml) 2 (10ml)	Tablets - 1/2 1

[1] Also recommended by the Public Service Task Force on Antipneumocystis Prophylaxis. CDC 1993 Sexually Transmitted Diseases Treatment Guidelines. *Morbidity and Mortality Weekly Report* 1993 Sep 24;42 (No. RR-14):1-102.

Parenteral:

IV:

Administer over 60 to 90 minutes. Avoid rapid infusion or bolus injection. Do not give IM. When administered by an infusion device, thoroughly flush all lines used to remove any residual TMP-SMZ. The following infusion systems have been tested and found satisfactory: Unit-dose glass containers; unit-dose polyvinyl chloride; polyolefin containers.

Vaginal Sulfonamides:

Vaginal tablets

Insert 1 tablet intravaginally each morning and evening for 10 days; repeat if necessary.

Vaginal cream

Insert 1 applicatorful intravaginally twice daily for 4—6 days. Therapy can then be reduced by 50—75%; repeat if necessary.

VI. Comparative Effectiveness of the Combination Sulfonamides

Table 7 describes clinical data for the drugs in this class.

Table 7. Additional Outcomes Evidence for Combination Sulfonamides

Study/Review	Sample	Duration	Results
Gill CJ, et al.[33]	-	Recommendations from WHO and the Joint UN programme on HIV/AIDS	• Infants with HIV infection are vulnerable to Pneumocystis carinii pneumonia (PCP) during their first year of life. WHO and the Joint United Nations Programme on HIV/AIDS now recommend that all children of HIV-positive mothers receive prophylactic cotrimoxazole against PCP from six weeks of age and continue this therapy until exposure through breast milk ceases and the infant is confirmed to be HIV-negative (rarely before one year of age). • Empirical prophylaxis invokes a trade-off between possible benefit to the infant versus the risk of resistance to antibiotics and antimalarials.
Khan AJ.[8]	n=320	12 Clinical Trials reviewed (meta-analysis)	• The role of single-dose therapy was evaluated by pooling data on 320 infants and children included in 12 clinical trials that differed from each other in many variables. • Single-dose therapy achieved an overall cure rate of 89%, but varied with different antimicrobial agents. Intramuscular aminoglycosides were the best (cure rate: 96%) closely followed by trimethoprim-sulfamethoxazole or a sulfa drug with a cure rate of 90%. The cure rate with amoxicillin (75%) was significantly less. Single-dose therapy was most effective (cure rate: 90%) in well-documented lower urinary tract infections (UTIs) and slightly less effective (cure rate: 89%) among those in whom upper UTI could not be excluded. In patients with a normal urinary tract, single-dose therapy was significantly more effective (cure rate: 93%) than in the group of 36 patients with a urinary tract malformation (cure rate: 69%). • Single-dose therapy can be used with confidence in patients with lower UTIs and in those with normal urinary tracts. In patients with abnormal urinary tracts and lower UTIs, single-dose therapy may be used with caution, preferably using aminoglycosides. • Further studies are required to establish a definitive role of single-dose therapy in patients with urinary tract malformation.
Armstrong EP.[10]			• This study was designed to evaluate the effectiveness of a urinary tract infection disease management program. • A pre-post design was used. One year of data before and after

			promoting the treatment guideline was compared. • A 300,000-member managed care organization introduced an antibiotic treatment guideline designed to change the antibiotic prescribing practices of community physicians. The study intervention was the promotion of a treatment guideline through mailings and face-to-face interventions by two disease management specialists. • The study demonstrated that prescribing patterns could be modified through treatment guideline distribution and face-to-face discussions. The study also found similar success rates across a range of antibiotics. • CONCLUSIONS: Consideration should be given to expanding the number of well-established (which include sulfonamides) antibiotics on the treatment guideline. Also, fluoroquinolones should be reserved for patients with sulfa allergies or failures with initial antibiotic treatment.
Nicolle, L. [12]			• Urinary tract infection is the most frequent bacterial infection. Acute uncomplicated urinary infection and acute non-obstructive pyelonephritis occur in young women with normal genitourinary tracts. • Empirical short-course therapy is preferred for the management of acute cystitis, but evolving resistance requires continuing reassessment of optimal antimicrobial selection. • Empirical trimethoprim or trimethoprim/sulfamethoxazole has been recommended, but increasing resistance to these agents suggests that pivmecillinam, nitrofurantoin and perhaps fosfomycin trometamol should be considered. • Although flouroquinolones are effective as short-course therapy, widespread empirical use of these agents should be discouraged because of potential promotion of resistance. For acute non-obstructive pyelonephritis, flouroquinolones are the empirical oral treatment of choice, although urine culture results should direct continuing therapy. • Treatment of complicated urinary infection is individualized, taking into consideration the underlying abnormality and susceptibilities of the infecting organism.
Nicolle L. [11]			• First-line treatment of acute uncomplicated UTI has traditionally involved a 3-day regimen of trimethoprim-sulfamethoxazole (TMP-SMX) or TMP alone for patients with sulfa allergies. • Increasing resistance among community-acquired *Escherichia coli* to TMP-SMX worldwide has led to a reassessment of the most appropriate empiric therapy for these infections. • Alternative first-line agents include the fluoroquinolones, nitrofurantoin, and fosfomycin. • Ideal antimicrobial agents for UTI management have primary excretion routes through the urinary tract to achieve high urinary drug levels.

Additional Evidence

Dose Simplification: No special release formulations are available for the sulfonamide medications, which would lower the frequency of administration of the sulfonamides. Typically the sulfonamides are dosed twice daily (Q12), as are other anti-infectives that might be used as alternatives for the same indications.

Stable Therapy: Not an issue for this drug category since most therapy is short term. However, if medications need to be changed because of resistance or adverse effects, no issues have been noted in the clinical data reviewed.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical literature relevant to use of the combination sulfonamide agents and their impact on physician visits.

VII. Conclusions

The oral sulfonamides have an established role in the treatment of otitis media, urinary tract infections, certain opportunistic infections in HIV, exacerbations of chronic bronchitis, and traveler's diarrhea. All sulfamethoxazole/trimethoprim agents in this class are available in a generic formulation. On the other hand, the clinical effectiveness of the vaginal sulfonamide agents in this class has been questioned, with the FDA and USP medical experts recommending against the use of vaginal sulfonamides.

Therefore, all brand products within the combination sulfonamide class are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over the alternatives in general use. The availability and effectiveness of the vaginal sulfonamide agents does not support benefits of their use.

VIII. Recommendations

No brand combination sulfonamide is recommended for preferred status. Additionally, the vaginal sulfonamide agents should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Miscellaneous Antibacterials
Single Entity Agents
AHFS 081228
October 27, 2004

I. Overview

The agents in this class are used for various infectious diseases, with primary use of the injectables reserved for hospitalized patients. Generic formulations are available for about half of the agents in the class, as indicated in Table 1.

This review encompasses all dosage forms and strengths.

Table 1. Single Entity Miscellaneous Antibacterials in this Review

Generic Name	Formulation	Example Brand Name
Bacitracin	Powder for Injection	*Baci-IM
Clindamycin HCL	Oral Capsules	*Cleocin HCL
Cleocin Palmitate	Oral Solution	*Cleocin Pediatric
Clindamycin Phosphate	Injection	*Cleocin Phosphate
Colistimethate Sodium	Injection (lyophilized cake)	*Coly-Mycin M, Colistin
Daptomycin	Injection	Cubicin
Lincomycin HCL	Oral Capsules, Injection	Lincocin, Lincoject
Polymyxin B Sulfate	Injection	*Polymyxin B Sulfate
Spectinomycin	Injection	Trobicin
Vancomycin HCL	Oral Pulvules, Oral Solution, Powder for Injection	*Vancocin (Pulvules not available as generic formulation)
Linezolid	Oral Tablets, Oral Suspension, Injection	Zyvox
Telithromycin	Oral	**Ketek

*Generic Available.
**Ketek (telithromycin), a new drug, was approved in August 2004. Per Alabama Medicaid P&T policy, telithromycin is eligible for review after it has been commercially available for at least 6 months. Telithromycin will be reviewed at a future time.

II. Evidence Based Medicine and Current Treatment Guidelines

Methicillin –Resistant *Staphylococcus Aureus* (MRSA)
MRSA is a gram-positive bacteria that grows in clusters like grapes. Growth of MRSA is not inhibited by methicillin or oxacillin and many other antibiotics. Antibiotic therapy of choice for infection caused by MRSA is intravenous vancomycin, with possible hospital admission.[1] Depending on sensitivity of the organism, other agents can be used, but resistance may rapidly emerge, especially to fusidic acid, rifampicin, and ciprofloxacin.[2] If agents other than vancomycin are preferred in treatment, combinations of at least two agents should be used. A second agent may also be considered for severe infections in which tissue penetration is not good. Oral vancomycin is not effective against MRSA.

Recently, the Centers for Disease Control (CDC) has made distinctions between community-associated MRSA versus infections and those acquired in hospitals and healthcare facilities.[56, 57] Some infections are often misdiagnosed as spider bites. Community-associated MRSA infections typically meet the following criteria:

- Diagnosis of MRSA made in the outpatient setting or by a culture positive for MRSA within 48 hours after admission to the hospital.
- Patient with no medical history of MRSA infection or colonization.

- Patient with no medical history in the past year of hospitalization, admissiton to a nursing home, skilled nursing facility, or hospice, dialysis, and surgery.
- Patient with no permanent indwelling catheters or medical devices that pass through the skin into the body.

Community-associated MRSA infections are typically limited to the skin and do not result in severe disease or death. On rare occasion, community-associated MRSA can cause severe illness even when treated quickly.

Proper hygiene is important in the prevention and transmission control of staph and MRSA infections. Those with MRSA infections should avoid sharing personal items with contact to infectious material, advise close family and friends to frequently wash their hands with soap and water, and keep infections of the skin covered with clean, dry bandages. In the hospital setting, contact precautions should be implemented for patients with MRSA infections. The CDC is currently working with several states and state health departments to better define the spectrum of disease and to develop surveillance systems for tracking these infections.

Most staph bacteria and MRSA are susceptible to several antibiotics. Commonly, staph skin infections can be treated without antibiotics by draining the sore. If antibiotics are prescribed, patients should complete the full course and call their doctors if the infection does not get better. Patients who are only colonized with staph bacteria or MRSA usually do not need treatment.

Health care workers can be colonized with *S. aureus,* indicating the presence of the organism without symptoms of illness. Colonization can occur in the nares, trachea, skin folds, rectum, and in open wounds. Infection occurs when tissue is invaded by *S. Aureus* with subsequent clinical symptoms. *S. aureus* permanently colonizes the anterior nares of about 20% to 30% of the general population.[1] Colonization with MRSA is not an indication for hospitalization. Proper infection control/prevention are important preventative measures and should include handwashing, gloving, linen handling, and environmental cleaning.

Although controlled studies provide little evidence of the effectiveness of treating carriers in reducing the spread of infection, it is reasonable to accept that a reduction in the number of sources of staphylococcal dispersal should reduce spread of infection.[2] The most effective treatment of nasal carriers and for skin disinfection is mupirocin ointment applied to the anterior nares three times daily for five days. Less effective alternatives, which can be considered after two courses of mupirocin, include chlorhexidine (1%), neomycin (0.5%) and chlorhexidine (0.1%), bacitracin (500units/g), or povidone-iodine (0.5%) creams or ointment. Topical use of antibiotics which may be required for systemic use (e.g. ciprofloxacin, fusidic acid, or gentamicin), should be forbidden. Mupirocin cream can be applied to infected MRSA lesions, but should not be used on large areas and treatment should not exceed five days.

Vancomycin can have serious side-effects, especially in elderly patients. Side effects include ototoxicity, nephrotoxicity, and allergic reactions such as fever and rash. Infusion of vancomycin can result in "red man syndrome", characteristic by flushing, hypotension, and tachycardia. Vancomycin given by mouth is not absorbed and is not effective against MRSA.

Once *S. aureus* has been identified, antibiotic susceptibilities should be performed. Oxacillin susceptibility by the Kirby Bauer technique is the preferred method of identifying MRSA.[1] Resistance to oxacillin also defines resistance to all penicillins. Cephalosporin susceptibilities should not be reported on MRSA isolates since all isolates are considered to be resistant in vivo, regardless of in vitro susceptibilities.

Infective Endocarditis

Treatment of endocarditis in adults depends on the clinical setting (acute versus subacute). Subacute empiric therapy typically consists of penicillin G (or ampicillin) plus gentamicin, with similar directed therapy for four weeks.[3] Acute disease in a normal host can be managed with oxacillin plus gentamicin empirically, with directed therapy of oxacillin or penicillin.

IV drug abusers should receive empiric therapy with vancomycin plus gentamicin, and directed therapy of either oxacillin plus gentamicin, piperacillin plus gentamicin, or ceftriaxone plus gentamicin, for a period of two to six weeks.

For patients with prosthetic valves, empiric therapy should include vancomycin plus gentamicin, with directed therapy of vancomycin or oxacillin (depending on the organism and susceptibilities) plus gentamicin and rifampin for six weeks. Alternative treatments include penicillin G plus gentamicin and ampicillin plus gentamicin.

Pseudomembranous Colitis (Antibiotic Associated Diarrhea)

Antibiotic associated diarrhea is the most common cause of diarrhea in hospitalized patients.[4] *Clostridium difficile* is frequently identified in patients with signs and symptoms of colitis. *C. difficile* diarrhea is a term used to describe a wide spectrum of diarrheal illnesses caused by the potent toxins produced by the organism. *C. difficile* is largely a nosocomial disease and is the most frequent cause of diarrhea in hospitalized patients. The cornerstone of this disease is identification of *C. difficile* toxins in the stool.

All types of antimicrobial agents have been implicated, leading to a wide range of clinical manifestations, from asymptomatic carrier state to severe pseudomembranous colitis. Those antibiotics with broad-spectrum coverage, in particular cephalosporins, extended-coverage penicillins, and clindamycin, are common culprits. Most cases respond to supportive measures and withdrawal of antibiotics. Patients with severe and persistent symptoms should receive antibiotic therapy, but relapses are common.

Treatment of this disease (according to the American College of Gastroenterology-ACG) include the following parameters:

- Discontinuation of antibiotics.
- Initiation of supportive therapy. Prophylactic antibiotic therapy should not be given routinely.
- Once the diagnosis of *C. difficile* diarrhea is confirmed and specific therapy is indicated, metronidazole therapy given orally is preferred.
- If diagnosis is highly likely and the patient is seriously ill, metronidazole may be given empirically before the diagnosis is established.
- Vancomycin given orally is reserved for the following conditions:
    - Failed therapy with metronidazole.
    - The identified organism is resistant to metronidazole.
    - The patient is allergic, cannot tolerate metronidazole, or is being treated with ethanol-containing solutions.
    - The patient is either pregnant or a child under 10 years of age.
    - The patient is critically ill because of *C. difficile*-associated diarrhea or colitis.
    - There is evidence suggesting the diarrhea is caused by *Staphylococcus aureus.*

Many antimicrobials have been used to treat *C. difficile* colitis. Oral vancomycin and metronidazole used for seven to ten days are considered first-line agents by most authors and current guidelines.[4] Multiple studies have reported initial response rates greater than 90% and comparable failure rates of 15% to 20%. Metronidazole at a dose of 250mg four times daily is recommended by most authors and ACG guidelines as the drug of choice for the initial treatment of *C. difficile* colitis. This recommendation is based on efficacy and on concerns about development of vancomycin-resistant strains. Disadvantages of metronidazole include a less desirable drug profile and contraindications in children and pregnant women. On the other hand, vancomycin at a dose of 125mg four times daily, achieves stool levels 20 times the required minimal inhibitory concentration required for the treatment of *C. difficile*.

III. Comparative Indications of the Single Entity Miscellaneous Antibacterials

Table 2. FDA-Approved Indications for the Single Entity Miscellaneous Antibacterials [5, 6, 7]

Drug	Lower RTI*	Anaerobic Infections	Bacterial Vaginosis	Acute or Chronic Infections	Skin and Suture Infections	Serious Infections	Acute Infections Caused by Pseudomonas aeruginosa	Gonorrhea	Enterocolitis and Pseudo-membranous Colitis	Vancomycin Resistant Organisms	Other
Bacitracin IM	✔ Pneumonia and Empyema in infants caused by staphylococci										
Clindamycin	✔ * Serious RTI and soft skin tissue infections caused by strep, staph, and pneumococci	✔ Septicemia, intra-abdominal, Ob-Gyn	✔								✔ Adjunctive Therapy for bone and joint infections
Colistimethate Sodium				✔ Gram-negative bacilli							
Daptomycin					✔ Complicated						
Lincomycin HCL						✔ * Resistant infections					
Polymyxin B Sulfate						✔ Second line	✔				

Drug	Lower RTI*		Bacterial Vaginosis	Acute or Chronic Infections	Skin and Suture Infections	Serious Infections	Acute Infections Caused by Pseudomonas aeruginosa	Gonorrhea	Enterocolitis and Pseudo-membranous Colitis	Vancomycin Resistant Organisms	
Spectinomycin								✔			
Vancomycin HCL						✔ MRSA			✔		Endocarditis
Linezolid	✔ Methicillin resistant strains (Nosocomial pneumonia), CAP				✔ Complicated and un-complicated, includes diabetic foot infections					✔	

*Reserved for penicillin allergic patients. .

IV. Pharmacokinetic Parameters of the Single Entity Miscellaneous Antibacterials

Table 3 lists the common pharmacokinetic parameters of the single entity miscellaneous antibacterials.

Table 3. Pharmacokinetic Parameters of the Single Entity Miscellaneous Antibacterials[5, 6, 7]

Drug	Mechanism of Action	Bioavailability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Bacitracin	Antibacterial activity derived from cultures of Bacillus subtilis; effective for staphylococcal infections. Has been given intrathecally.	Absorption rapid and complete. Widely distributed in all body organs and is demonstrable in ascitic and pleural fluids.	-	-	-	Renal; glomerular filtration	N/A
Clindamycin HCL	Inhibits bacterial protein synthesis at the level of the bacterial ribosome.	Rapid absorption of oral dose virtually complete (90%).	-	Liver	Yes	3.6.% eliminated in feces; 10% eliminated in urine	~2.4 hours
Cleocin Palmitate HCL	Inhibits bacterial protein synthesis at the level of the bacterial ribosome.	Widely distributed in body fluids and tissues (including bones).	-	Liver	Yes	~10% eliminated in urine	~2 hours
Clindamycin Phosphate,	Inhibits bacterial protein synthesis at the level of the bacterial ribosome.	Systemic absorption ~ 30% (range 6% - 70%). 90% of an oral dose is absorbed from the GI tract.	-	Liver	Yes	10% of oral dose is excreted in urine and 3.6% in feces	Serum half-life is 2-3 hours
Colisti-methate Sodium	Surface active agent which penetrates into and disrupts the bacterial cell membrane.	Not absorbed from the GI tract, must be given parenterally. IV administration gives higher peak serum concentrations that decline more rapidly than those with IM administration.	-	Kidney	Yes	Renal; glomerular filtration	2 – 3 hours
Daptomycin for Injection	The mechanism of action of daptomycin is distinct from any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis,	<table><tr><th>mg/kg</th><th>C_{max} (mcg/mL)</th><th>T_{max}[1] (h)</th><th>AUC_{0-24} (mcg·h/mL)</th></tr><tr><td>4 (n = 6)</td><td>57.8</td><td>0.8</td><td>494</td></tr><tr><td>6 (n = 6)</td><td>98.6</td><td>0.5</td><td>747</td></tr><tr><td>8 (n = 6)</td><td>133</td><td>0.5</td><td>1130</td></tr></table>	Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The	It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the CYP 450 system. It	-	Primarily renal; 78% of a dose was recovered in the urine, 5.7% from feces.	-

	which results in bacterial cell death. The in vitro spectrum of daptomycin activity encompasses most clinically relevant gram-positive pathogenic bacteria. Daptomycin retains potency against antibiotic-resistant gram-positive bacteria, including isolates resistant to methicillin, vancomycin, and linezolid.	[1]Median (minimum, maximum).	mean serum protein binding of daptomycin was approximately 92% in healthy adults after the administration of 4 or 6mg/kg.	is unknown whether daptomycin is a substrate of the CYP 450 system.			
Lincomycin HCL	Lincomycin has bacteriostatic or bactericidal action, depending on the concentration of the drug at the site of infection.	20-30% of an oral dose is rapidly absorbed from the GI tract; food delays or decreases the extent of absorption of the drug.	-	Liver	-	Both drug and metabolites are excreted in urine, bile, and feces. Following oral admin, 1-31% of the dose is excreted in urine and as much as 40% is excreted in feces.	Plasma half-life is 4-6.4 hours with normal renal function.
Polymyxin B Sulfate	Polymyxin B sulfate is bactericidal. The drug binds to phosphate groups in the lipids of bacterial cytoplasmic membrane and acts as a cationic detergent, altering the osmotic barrier of the membrane and causing leakage of essential metabolites.	The drug is not absorbed from the GI tract except in infants who may absorb up to 10% of a dose. After IM administration, peak serum concentrations of 1-8mcg/mL are obtained within approximately 2 hours. Detectable amounts of the drug remain in the serum for up to 12 hours.	50% is reversibly bound to phospholipids of cell membranes in the liver, kidneys, heart, muscle, brain, and other tissues. The drug is not highly protein bound to serum proteins.	-	-	60% of a dose is excreted unchanged into the urine by glomerular filtration. Information is lacking on the fate of the other 40% of the dose.	Serum half-life is reported to be 4.3-6 hours in adults with normal renal function
Spectino-mycin	Spectinomycin is bacteriostatic in action and appears to inhibit protein synthesis in susceptible	The drug is not absorbed from the GI tract, however, drug is rapidly absorbed following IM administration.	The drug is not substantially bound to plasma proteins.	-	-	Within 48 hours, 70-100% of a single IM dose of spectinomycin is	Plasma half-life is reported to be 1.2-2.8 hours in adults.

	bacteria by binding to 30S ribosomal subunits					excreted in the urine by glomerular filtration.	
Vancomycin HCL	Vancomycin is bactericidal and binds to the bacterial cell wall causing blockage of glycopeptide polymerization. This effect products immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.	Vancomycin is usually not appreciably absorbed from the GI tract; limited data suggest that clinically important serum concentrations of the drug may result following enteral or oral administration of vancomycin in some patients with colitis, particularly those with renal impairment.	At a concentration of 10-100mcg/mL in vitro, vancomycin is reportedly 52-60% bound to serum proteins.	-	-	Parenterally administered vancomycin is excreted primarily by glomerular filtration. More than 80% of a single IV dose is excreted within 24 hours.	Serum elimination half-life of vancomycin in adults with normal renal function has been reported to average 4-6 hours. Accumulation occurs after 2-3 days of IV administration at 6 or 12-hour intervals.
Linezolid	Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against most strains of streptococci. It acts early in translation by binding to a site on the bacterial 23S ribosomal RNA of the 50S subunit and preventing the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.	The drug is well absorbed following oral administration (absolute bioavailability 100%) and is readily distributed to well-perfused tissues.	31%	Linezolid is metabolized primarily via oxidation to 2 inactive metabolites; it is not metabolized to any extent by the cytochrome P-450 enzyme system.	No	Nonrenal clearance accounts for approximately 65% of the total clearance of linezolid; 30% appears in the urine as linezolid.	6.4 hours

V. Drug Interactions of the Single Entity Miscellaneous Antibacterials

Table 4 describes the Level 1 and Level 2, most significant, drug interactions with the agents in this class. No Level 1 or 2 interactions are documented for linezolid.

Table 4. Drug Interactions of the Single Entity Miscellaneous Antibacterials[8]

Drug	Significance	Interaction	Mechanism
Polypeptide Antibiotics	Level 2	Nondepolarizing muscle relaxants (atracurium, pancuronium, vercuronium) and polypeptide antibiotics (bacitracin, colistimethate, polymyxin B, vancomycin)	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants. The combination should be avoided if possible.
Clindamycin and Lincomycin	Level 2	Clindamycin, lincomycin and aluminum salts (aluminum carbonate, aluminum hydroxide, aluminum phosphate, kaopectate, etc.)	GI absorption is decreased for lincomycin and delayed for clindamycin when they are administered with Kaolin-pectin antidiarrheals.
Clindamycin and Lincomycin	Level 2	Nondepolarizing muscle relaxants (atracurium, pancuronium, vercuronium) and lincosamides (clindamycin and lincomycin)	Apparent potentiation or additive pharmacologic actions. The lincosamides may enhance the actions of the nondepolarizing muscle relaxants, possibly contributing to profound and severe respiratory depression. The combination should be avoided if possible.

Other drug interaction data:

- **Daptomycin**
  Daptomycin does not inhibit or induce cytochrome P450 isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4, and pharmacokinetic interactions with drugs metabolized by these isoenzymes are unlikely.[6] Serum concentrations and AUC of daptomycin and aztreonam were not substantially altered after concurrent use of single doses of both together.

  Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK.[7] There were no reports of skeletal myopathy in a placebo-controlled phase 1 trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with daptomycin (4mg/kg once every 24 hours) for 14 days. Experience with coadministration of HMG-CoA reductase inhibitors and daptomycin in patients is limited, therefore, consider temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving daptomycin.

  Coadministration of daptomycin (6mg/kg/day for 5 days) and warfarin (25mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the international normalized ratio (INR) was not significantly altered. As experience with the coadministration of daptomycin and warfarin is limited to volunteer studies, monitor anticoagulant activity in patients receiving daptomycin and warfarin for the first several days after initiating daptomycin therapy.

  Coadministration of daptomycin and tobramycin may result in a pharmacokinetic interaction.[6] Mean maximum plasma concentration and AUC of daptomycin were increased by approximately 13% and 9%, respectively, while mean maximum plasma concentration and AUC of tobramycin were decreased by approximately 11 and 7%, respectively, when both drugs were used together.

- **Spectinomycin**
  Multiple references do not list drug interactions for spectinomycin.[5-8] The drug is given for the treatment of gonorrhea and is typically administered in a single dose. It is unlikely significant drug interactions would occur.

- **Bacitracin**
  Concomitant use of bacitracin and aminoglycosides may result in increased risk of respiratory paralysis and renal dysfunction.[7] This same interaction occurs with polymyxin B, colistimethate, and vancomycin and can result in the same risks.

- **Vancomycin**
  Vancomycin and anesthetics have been associated with erythema and histamine-like flushing in children.[7] Also, concomitant use of vancomycin and other neurotoxic/nephrotoxic agents requires careful monitoring.

VI. Adverse Drug Events of the Single Entity Miscellaneous Antibacterials

Adverse events reported for colistimethate are similar to those reported with polymyxin B.[6] Vancomycin is very irritating to tissue and causes necrosis when given IM. When vancomycin is administered IV, care must be taken to avoid extravasation. Additionally, hypersensitivity reactions occur in 5-10% of patients receiving vancomycin.[6] Table 5 compares the adverse events for the anti-infective agents in this class.

Black Box Warnings: Bacitracin and Polymyxin B Sulfate

Bacitracin[7]

Nephrotoxicity:

Parenteral (IM) bacitracin may cause renal failure due to tubular and glomerular necrosis. Restrict use to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible. Use only where laboratory facilities are adequate and constant supervision is possible.

Carefully determine renal function prior to therapy, and daily during therapy. Do not exceed the recommended daily dose, and maintain fluid intake and urinary output at proper levels to avoid renal toxicity. If renal toxicity occurs, discontinue the drug. Avoid the concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, colistin and neomycin.

Polymyxin B Sulfate[7]

When this drug is given intramuscularly or intrathecally, administer only to hospitalized patients to provide constant physician supervision.

Carefully determine renal function; reduce dosage in patients with renal damage and nitrogen retention. Patients with nephrotoxicity due to polymyxin B sulfate usually show albuminuria, cellular casts and azotemia. Diminishing urine output and a rising BUN are indications to discontinue therapy.

Neurotoxic reactions may be manifested by irritability, weakness, drowsiness, ataxia, perioral paresthesia, numbness of the extremities and blurring of vision. These are usually associated with high serum levels found in patients with impaired renal function or nephrotoxicity. Avoid concurrent use of other nephrotoxic and neurotoxic drugs, particularly kanamycin, streptomycin, paromomycin, colistin, tobramycin, neomycin and gentamicin.

The drug's neurotoxicity can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia or muscle relaxants.

Table 5. Common Adverse Events (%) Reported for the Single Entity Miscellaneous Antibacterials[5-7]

Adverse Event	Bacitracin[1]	Clindamycin[2]	Colistimethate[3]	Linco-mycin	Polymyxin B Sulfate[4]	Dapto-mycin	Spectino-Mycin	Vanco-mycin[5]	Linezolid
Body as a Whole									
Ataxia			✔		✔				
Malaise									
Respiratory Arrest			✔	✔					
Cardiovascular									
Edema									
Hypotension		✔		✔		✔		✔	
Hypertension									✔
Digestive System									
Abdominal Pain				✔					✔
Nausea / Vomiting	✔	✔		✔		✔	✔	✔	✔
Diarrhea	✔	✔	✔	✔		✔			✔
Epigastric distress		✔	✔			✔			
Appetite decrease	✔	✔							
Central Nervous System									
Dizziness/Vertigo			✔	✔	✔	✔	✔	✔	✔
Fatigue									
Fever	✔	✔	✔		✔	✔	✔	✔	✔
Headache				✔		✔			
Meningeal Signs									✔
Raised Intracranial Pressure									
Collapse									
Confusion			✔		✔				
Drowsiness					✔				
Hearing loss								✔	
Hepatic									
Abnormal LFTs (incr.)		✔		✔		✔	✔		✔
Hepatitis							(multiple		
Jaundice							doses)		
Hepatic failure									
Skin and Appendages									
Alopecia									
Rash	✔	✔	✔	✔	✔	✔		✔	✔
Pruritus		✔	✔	✔		✔		✔	✔
Hematologic									
Neutropenia		✔		✔				✔	
Agranulocytosis		✔		✔					
Bone marrow tox.	✔								
Leukopenia		✔		✔		✔			✔
Thrombocytopenia						✔		✔	✔
Renal									
Abnormal kidney fxn	✔		✔		✔		✔	✔	
Acute kidney failure	(azotemia)				(azotemia)	✔	(multiple		
Albuminuria	✔				✔		doses)		
Cylindruria	✔				✔				
Other									
Angioedema				✔					
Convulsions			✔		✔				
Pain at injection site		✔		✔	✔	✔	✔	✔	
? blood conc. of drug	✔				✔				
Rectal itching/burning	✔								
Taste Alteration		✔							✔
Polyarthritis		✔							
Tingling of extremities			✔						
Fungal Infections						✔			✔
UTI						✔			
Redman Syndrome								✔	

✔ Adverse events reported; specific percentages not available.

[1]Bacitracin: The most important toxic effect of IM bacitracin therapy is renal tubular and glomerular necrosis.

[2]Clindamycin: GI events (diarrhea and colitis) frequently occur with oral, IM, and IV clindamycin and may be severe enough to cause discontinuation of the drug.

[3] Nephrotoxicity and neurotoxicity are the most serious adverse events of colistimethate and are most likely to occur when the drug is used in higher than recommended dosages or in patients with impaired renal function.

[4] Polymyxin B: Nephrotoxicity and neurotoxicity are the most serious adverse events of parenteral polymyxin B.

[5] Vancomycin: Ototoxicity and nephrotoxicity are the most serious adverse events of parenteral vancomycin therapy.

VII. Dosing and Administration for the Single Entity Miscellaneous Antibacterials

Table 6. Dosing for the Single Entity Miscellaneous Antibacterials[5-7]

Drug	Availability	Dose /Frequency/Duration
Bacitracin	Powder for injection: 50,000 units	For IM use only. Give in upper outer quadrant of buttocks, alternating sides and avoiding multiple injections in the same region because of transient pain following injection. Recommended dosages should not be exceeded. Should not be administered longer than 12 days. **Infants < 2.5kg:** 900units/kg/24 hours, in 2 or 3 divided doses. **Infants > 2.5kg:** 1000units/kg/24 hours, in 2 or 3 divided doses. **Adults:** Use in adults is not indicated.
Clindamycin HCl Clindamycin Palmitate (pediatric) Clindamycin Phosphate	Capsules: 75mg, 150mg, and 300mg Granules for oral solution: 75mg/5ml, 100ml Injection: 150mg/ml	If significant diarrhea occurs during therapy, the antibiotic should be discontinued. For anaerobic infections, the parenteral form should be used initially, followed by oral therapy. For B-hemolytic streptococcal infections, treatment should continue for at least 10 days. Oral clindamycin should be taken with a full glass of water or with food to avoid esophageal irritation. Clindamycin absorption is not affected by food. **Adults:** **Serious infections:** 150 to 300mg every 6 hours. **Prophylaxis of bacterial endocarditis (PCN allergic patients):** 600mg orally 1 hour prior to the procedure; if unable to take oral, use 600mg IV 30min prior to procedure. **More severe infections:** 300 to 450mg every 6 hours. **Children:** **<u>Clindamycin HCl:</u>** **Serious infections:** 8 to 16mg/kg/day divided into 3 or 4 equal doses. **More severe infections:** 16 to 20mg/kg/day divided into 3 or 4 equal doses. **<u>Clindamycin palmitate:</u>** **Serious infections:** 8 to 12mg/kg/day divided into 3 or 4 equal doses. **Severe infections:** 13 to 25mg/kg/day divided into 3 or 4 equal doses. In children weighing = 10 kg, administer 37.5mg 3 times daily as the minimum dose. **<u>Parenteral:</u>** May be administered IM or IV. Single IM injections = 600mg are not recommended.

<table>
<tr><td></td><td></td><td>Adults:
Serious infections:
Due to aerobic gram-positive cocci and the more sensitive anaerobes: 600 to 1200mg/day in 2 to 4 equal doses.

More severe infections:
Particularly those due to B. fragilis, Peptococcus sp. or Clostridium sp. other than C. perfringens: 1.2 to 2.7g/day in 2 to 4 equal doses. For more serious infections, these doses may have to be increased.

<u>In life-threatening situations:</u>
Due to aerobes or anaerobes, doses of 4.8g/day have been given IV to adults.

Children (> 1 month of age to 16 years):
20 to 40mg/kg/day in 3 or 4 equal doses, depending on the severity of infection. Alternatively, children may be dosed based on body surface area:

Serious infections:
350mg/m^2/day;

More serious infections:
450mg/m^2/day.

Neonates (< 1 month of age):
15 to 20mg/kg/day in 3 to 4 equal doses.

CDC recommendation for acute pelvic inflammatory disease[10]:
900mg IV every 8 hours plus gentamicin loading dose 2mg/kg IV or IM, followed by 1.5mg/kg every 8 hours. Parenteral therapy may be discontinued 24 hours after a patient improves. After discharge from hospital, continue with oral doxycycline 100mg 2 times a day for 10 to 14 days total. Alternatively, continue with oral clindamycin 450mg 4 times daily for 14 days.</td></tr>
<tr><td>Colistimethate Sodium</td><td>Injection (lyophilized cake): 150mg colistin (as colistimethate sodium) for reconstitution</td><td>For IM or IV use.

Adults and children:
2.5 to 5mg/kg/day in 2 to 4 divided doses for patients with normal renal function, depending upon the severity of the infection. Reduce the daily dose in the presence of any renal impairment as indicated below.

<table>
<tr><td colspan="7">Suggested Modification of Colistimethate Dosage Schedules for Adults with Impaired Renal Function[7]</td></tr>
<tr><td colspan="3">Renal function</td><td colspan="4">Dosage</td></tr>
<tr><td>Degree of impairment</td><td>Plasma creatinine (mg/dl)</td><td>Urea clearance % (of normal)</td><td>Dose[1] (mg)</td><td>Frequency (times per day)</td><td>Total daily dose (mg)</td><td>Approx. daily dose (mg/kg)</td></tr>
<tr><td>Normal</td><td>0.7 - 1.2</td><td>80 – 100</td><td>100 - 150</td><td>4 to 2</td><td>300</td><td>5</td></tr>
<tr><td>Mild</td><td>1.3 - 1.5</td><td>40 – 70</td><td>75 - 115</td><td>2</td><td>150 - 230</td><td>2.5 - 3.8</td></tr>
<tr><td>Moderate</td><td>1.6 - 2.5</td><td>25 – 40</td><td>66 - 150</td><td>2 or 1</td><td>133 - 150</td><td>2.5</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>Severe</td><td>2.6 - 4</td><td>10 – 25</td><td>100 - 150</td><td>q 36 h</td><td>100</td><td>1.5</td></tr>
</table>
[1]Suggested unit dose is 2.5 to 5mg/kg; increase time interval between injections in presence of impaired renal function.

IV administration:
Direct intermittent administration:
Inject one-half the total daily dose over a period of 3 to 5 minutes every 12 hours.

Continuous infusion:
Slowly inject one-half the daily dose over 3 to 5 minutes. Add the remaining half of the total daily dose of colistimethate to one of the following: 0.9%Sodium Chloride; 5% Dextrose in Water; 5% Dextrose with 0.9% Sodium Chloride;5% Dextrose with 0.45% Sodium Chloride; 5% Dextrose with 0.225% Sodium Chloride; Lactated Ringer's solution. Swirl gently to avoid frothing.
Administer by slow IV infusion starting 1 to 2 hours after the initial dose over the next 22 to 23 hours in the presence of normal renal function. In the presence of impaired renal function, reduce infusion rate. Choice of IV solution and volume to be employed are dictated by requirements of fluid and electrolyte management.
</td></tr>
<tr><td>Daptomycin</td><td>Powder for injection, lyophilized: 250mg, 500mg</td><td>
Complicated skin and skin structure infections:
Administer daptomycin 4mg/kg over a 30-minute period by IV infusion in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days. In phase 1 and 2 clinical studies, creatine phosphokinase (CPK) elevations appeared to be more frequent when daptomycin was dosed more frequently than once daily. Therefore, do not dose daptomycin more frequently than once a day.
Renal function impairment:
Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance (CCr) less than 30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). When possible, administer daptomycin following hemodialysis on hemodialysis days.

<table>
<tr><th colspan="2">Daptomycin Dosage in Adult Patients with Renal Impairment [7]</th></tr>
<tr><th>Creatinine clearance</th><th>Dosage regimen</th></tr>
<tr><td>= 30mL/min</td><td>4mg/kg once every 24 hours</td></tr>
<tr><td>< 30mL/min, including hemodialysis or CAPD</td><td>4mg/kg once every 48 hours</td></tr>
</table>
</td></tr>
<tr><td>Lincomycin HCL</td><td>Capsules: 500mg
Injection: 300mg/ml</td><td>
If significant diarrhea occurs during therapy, this antibiotic should be discontinued. Oral lincomycin should be taken at least 1-2 hours before or after eating to ensure optimum absorption.

Oral:
Adults:
Serious infections:
500mg every 8 hours.

More severe infections:
= 500mg every 6 hours. With B-hemolytic streptococcal infections, continue treatment for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

Children > 1 month of age:
Serious infections:
30mg/kg/day (15mg/lb/day) divided into 3 or 4 equal doses.
</td></tr>
</table>

More severe infections:
60mg/kg/day (30mg/lb/day) divided into 3 or 4 equal doses.

IM:
IM administration is well tolerated.

Adults:
Serious infections:
600mg every 24 hours.

More severe infections:
600mg every 12 hours or more often.

Children > 1 month of age:
Serious infections:
10 mg/kg (5 mg/lb) every 24 hours.

More severe infections:
10 mg/kg (5 mg/lb) every 12 hours or more often.

IV:
Dilute to 1g/100mL (minimum) and infuse over a period of at least 1 hour. Severe cardiopulmonary reactions have occurred when given at greater than the recommended concentration and rate. IV administration in 250 to 500mL of 5% Dextrose in Water or Normal Saline produces no local irritation or phlebitis.

Lincomycin Infusion Rates [7]		
Dose	Volume diluent (mL)	Time (hr)
600mg	100	1
1g	100	1
2g	200	2
3g	300	3
4g	400	4

Adults:
Determine dose by the severity of the infection.

Serious infections:
600 mg to 1g every 8 to 12 hours.

Severe to life-threatening situations:
Doses of 8g/day have been given.

Maximum recommended dose:
8g/day.

Children > 1 month of age:
Infuse 10 to 20mg/kg/day (5 to 10mg/lb/day), depending on severity of infection, in divided doses as described above for adults.

Polymyxin B Sulfate	Injection: 500,000units	**IV:** Dissolve 500,000units polymyxin B sulfate in 300 to 500 ml of 5% Dextrose in Water for continuous IV drip. **Adults and children:** 15,000 to 25,000units/kg/day in individuals with normal renal function. Reduce this amount from 15,000units/kg downward for individuals with renal impairment. Infusions may be given every 12 hours; however, the total daily dose must not exceed 25,000units/kg/day. **Infants:** Those with normal renal function may receive up to 40,000units/kg/day. **IM:** Not recommended routinely because of severe pain at injection sites, particularly in infants and children. Dissolve 500,000units in 2ml sterile distilled water (Water for Injection, USP) or sterile physiologic saline (Sodium Chloride Injection) or 1% procaine HCl solution. **Adults and children:** 25,000 to 30,000units/kg/day. Reduce dosage in the presence of renal impairment. Dosage may be divided and given at either 4 or 6 hour intervals. **Infants:** Those with normal renal function may receive up to 40,000units/kg/day. Note: Doses as high as 45,000units/kg/day have been used in limited clinical studies in treating premature and newborn infants for sepsis caused by *Pseudomonas aeruginosa*. **Intrathecal:** A treatment of choice for *P. aeruginosa* meningitis. Dissolve 500,000units in 10ml sterile physiologic saline for a concentration of 50,000units/ml. **Adults and children (> 2 years of age):** 50,000units once daily intrathecally for 3 to 4 days, then 50,000units once every other day for at least 2 weeks after cultures of the CSF are negative and glucose content has returned to normal. **Children (< 2 years of age):** 20,000units once daily, intrathecally for 3 to 4 days or 25,000 units once every other day. Continue with a dose of 25,000 units once every other day for at least 2 weeks after cultures of the CSF are negative and glucose content has returned to normal.
Spectinomycin	Powder for injection: 400mg/ml when reconstituted	For IM use only. Shake vials vigorously immediately after adding diluent and before withdrawing dose. Inject 5ml (2g) IM deep into upper outer quadrant of gluteal muscle. Also recommended for treatment after failure of previous antibiotic therapy. In geographic areas where antibiotic resistance is prevalent, initial treatment with 4g (10ml) IM is preferred, and may be divided between 2 gluteal injection sites. **CDC recommended treatment schedules for gonorrhea:[11]** **Uncomplicated urethral, endocervical or rectal gonococcal infections, alternative regimen:** For patients who cannot take cephalosporins or fluoroquinolones, the preferred alternative is spectinomycin 2g IM as a single dose. Children = 45kg (100lbs) should receive adult regimens. Children <45kg with

		uncomplicated vulvovaginitis, cervicitis, urethritis, pharyngitis or proctitis and who cannot tolerate ceftriaxone may receive a single 40mg/kg IM dose (max: 2g). **Gonococcal infections in pregnancy:** Treat pregnant women allergic to cephalosporins with a single 2g IM dose of spectinomycin. **Disseminated gonococcal infection:** Spectinomycin 2g IM every 12hours may be used as an alternative to fluoroquinolones in patients allergic to B-lactams.
Vancomycin HCL	Pulvules: 125mg and 250mg Powder for oral solution: 1g Powder for injection: 500mg, 1g, 5g, 10g	**<u>Oral:</u>** **Adults:** 500mg to 2g/day given in 3 or 4 divided doses for 7 to 10 days. Alternatively, dosages of 125mg 3 or 4 times daily for *C. difficile* colitis may be as effective as the 500mg dose regimen. **Children:** 40mg/kg/day in 3 or 4 divided doses for 7 to 10 days. Do not exceed 2g/day. **Preparation of solution:** Add 115ml distilled or deionized water to the 10g container. Each 6ml of solution provides approximately 500mg vancomycin. The contents of the 1g vial may be mixed with distilled or deionized water (20ml). When reconstituted, each 5ml contains approximately 250mg vancomycin. Mix thoroughly to dissolve. The appropriate oral solution dose may be diluted in 1oz of water and given to the patient to drink. Common flavoring syrups may be added to the solution to improve the taste for oral administration. The diluted material may be administered via nasogastric tube. **<u>Parenteral:</u>** Administer each dose over at least 60 minutes. Intermittent infusion is the preferred administration method. **Adults:** 500mg IV every 6 hours or 1g every 12 hours. **Children:** 10mg/kg per dose given every 6 hours. **Infants and neonates:** Initial dose of 15mg/kg, followed by 10mg/kg every 12hours for neonates in the first week of life and every 8 hours thereafter up to the age of 1 month. **Prevention of bacterial endocarditis:[12]** **GU/GI procedures (high-risk, penicillin-allergic patients):** 1g IV over 1 to 2 hours (children, 20mg/kg) plus gentamicin 1.5mg/kg IV or IM for both adult (not to exceed 120mg) and children. Complete injection or infusion within 30 minutes of starting procedure. **Moderate-risk, penicillin-allergic patients:** 1g IV over 1 to 2 hours (children 20mg/kg). Complete infusion within 30 minutes of starting procedure.

<table>
<tr><td></td><td></td><td>Adjust dosage; check serum levels regularly. In premature infants and the elderly, dosage reduction may be necessary caused by decreasing renal function.

For most patients, if creatinine clearance (CCr) can be measured or estimated accurately, the dosage may be calculated by using the following table.

<table>
<tr><th colspan="2">Vancomycin Dosage in Impaired Renal Function[7]</th></tr>
<tr><th>CCr (ml/min)</th><th>Dose (mg/24 hr)</th></tr>
<tr><td>100</td><td>1545</td></tr>
<tr><td>90</td><td>1390</td></tr>
<tr><td>80</td><td>1235</td></tr>
<tr><td>70</td><td>1080</td></tr>
<tr><td>60</td><td>925</td></tr>
<tr><td>50</td><td>770</td></tr>
<tr><td>40</td><td>620</td></tr>
<tr><td>30</td><td>465</td></tr>
<tr><td>20</td><td>310</td></tr>
<tr><td>10</td><td>155</td></tr>
</table>
</td></tr>
<tr><td>Linezolid</td><td>Tablets: 400mg and 600mg
Powder for oral suspension: 100mg/5ml, 240ml
Injection: 2mg/ml</td><td>Administer without regard to meals.

<table>
<tr><th colspan="4">Linezolid Dosage Guidelines[7]</th></tr>
<tr><th rowspan="2">Infection[1]</th><th colspan="2">Dosage and route of administration</th><th rowspan="2">Recommended duration of treatment (consecutive days)</th></tr>
<tr><th>Pediatric patients[2] (birth through 11years of age)</th><th>Adults and adolescents (12 years and older)</th></tr>
<tr><td>Complicated skin and skin-structure infections</td><td rowspan="3">10mg/kg IV or oral[3] q 8 h</td><td rowspan="3">600mg IV or oral[3] q 12 h</td><td rowspan="3">10 to 14</td></tr>
<tr><td>Community-acquired pneumonia, including concurrent bacteremia</td></tr>
<tr><td>Nosocomial pneumonia</td></tr>
<tr><td>Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia</td><td>10mg/kg IV or oral[3] q8 h</td><td>600mg IV or oral[3] q12 h</td><td>14 to 28</td></tr>
<tr><td>Uncomplicated skin and skin-structure infections</td><td>< 5 yrs: 10mg/kg oral[3] q8h
5 to 11 yrs: 10mg/kg oral[3] q12h</td><td>Adults : 400 mg oral[3] q12h
Adolescents : 600mg oral[3] q12h</td><td>10 to 14</td></tr>
</table>
</td></tr>
</table>

		[1]Due to the designated pathogens. [2]Neonates younger than 7 days: Most preterm neonates younger than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Initiate these neonates with a dosing regimen of 10mg/kg twice daily. Consider the use of 10mg/kg 3 times daily regimen in neonates with a suboptimal clinical response. Give all neonatal patients 10mg/kg 3 times daily by 7 days of life. [3]Oral dosing using either linezolid tablets or linezolid for oral suspension. Treat adult patients with methicillin-resistant *S. aureus* (MRSA) infection with linezolid 600mg/12 hours. No dose adjustment is necessary when switching from IV to oral administration. Patients who are started on IV therapy may be switched to either tablets or oral suspension when clinically indicated.

Special Dosing Considerations

Table 7. Special Dosing Considerations for the Single Entity Miscellaneous Antibacterials[5-8]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed?
Bacitracin	Contraindicated in patients with renal insufficiency.	No	Yes	C-Not recommended for use during pregnancy	N/A, IM only
Clindamycin	Yes-only in severe renal disease	Yes-only in severe hepatic disease	Yes-infants and neonates	B	Available in capsules, oral solution, and injection.
Colistimethate Sodium	Yes-see Table 6	No	Has been administered to neonates, infants, children, and adolescents; the adverse event profile in pediatric patients is similar to that in adults.	C	N/A, IM or IV only
Daptomycin	Yes-see Table 6	No	Safety and efficacy not established in children younger than 18 years of age.	B	N/A, IV only
Lincomycin HCL	When required, an appropriate dose is 25% to 30% of that recommended for patients with normal renal function.	No	Safety and efficacy of lincomycin in infants younger than one month of age has not been established.	B	Per the manufacturer, no data is available on alternative administration of lincomycin capsules, such as opening the capsules and mixing the contents with juice, or administration of the contents per tube.
Polymyxin B Sulfate	Yes-obtain serum drug concentrations and adjust dose	No	Children and infants	B	N/A, injection only
Spectinomycin	No	No	Although safety and efficacy of spectinomycin	B	N/A, injection only

			in pediatric patients have not been established, the CDC and American Academy of Pediatrics recommend the drug's use for the treatment of gonococcal infections in children with hypersensitivities to cephalosporins.		
Vancomycin HCL	Yes, see Table 6.	No	Neonates, infants, and children	B	Available in pulvules, oral solution, and injection.
Linezolid	Use with caution in severe renal disease.	Use with caution in severe renal disease.	Safety and efficacy of linezolid in pediatric patients is supported by adequate and well-controlled studies in adults, and pharmacokinetic studies in children from birth to 17 years of age. Data is also available from controlled and uncontrolled studies in children.	C	Available in tablets, oral suspension, and injection.

VIII. Comparative Effectiveness of the Single Entity Miscellaneous Antibacterials

Table 8. Outcomes Evidence for Single Entity Miscellaneous Antibacterials

Study	Sample	Design	Results
Bacitracin irrigation for laparoscopic gastric bypass[13]	n=66	Non-controlled, consecutive enrollment.	All patients received preoperative levofloxacin 500 mg IV, metronidazole 500 mg IV, and peritoneal irrigation with 1000 mL normal saline containing bacitracin 50 000 units and kanamycin 1 g. • Culture results were positive for 22.7% of patients. • After 9 months, no patient experienced clinical infection or required an extension of antibiotics beyond the first 24 hours.
Bacitracin, Clotrimazole, and Gentamicin lozenge for radiation-induced mucositis[14]	n=137	Multicenter, prospective, randomized, double-blind, placebo-controlled trial.	Patients with head and neck cancer requiring radiation were randomized to receive either antimicrobial or placebo lozenge. • Median time to development of severe mucositis from start of radiotherapy was 3.61 weeks in the active group vs. 3.96 weeks in the placebo group (p=0.61).
Clindamycin ± cephalosporin vs. Ampicillin/Sulbactam for aspiration pneumonia and lung abscess[15]	n=70	Open-label, multicenter, prospective, randomized, comparative trial.	• Duration of therapy was 22.7 days in the ampicillin/sulbactam group vs. 24.1 days in the clindamycin group. • Clinical response at end of therapy in the ampicillin/sulbactam group was 73% vs. 66.7% in the clindamycin group. • Clinical response at 7 to 14 days after therapy was 65.7% in the ampicillin/sulbactam group vs. 63.5% in the clindamycin group.
Clindamycin for abnormal vaginal flora and bacterial vaginosis in asymptomatic pregnant women[16]	n=485	Randomized, double-blind, placebo-controlled trial.	Women at 12 to 22 weeks gestation with abnormal vaginal flora or bacterial vaginosis according to Nugent's criteria received clindamycin 300 mg or placebo twice daily for 5 days. • Incidence of miscarriage or preterm delivery was 13/244 in the clindamycin group vs. 38/241 in the placebo group (95% CI, 5 to 15.8%; p=0.0003).
Clindamycin vs. Piperacillin/Tazobactam for nosocomial pneumonia in cancer patients[17]	n=53	Prospective, randomized trial.	Patients received clindamycin 900 mg plus aztreonam 2 g IV every 8 hours or piperacillin/tazobactam 4.5 g IV every 6 hours. All patients received amikacin 500 mg IV every 12 hours for the first 48 hours. • Response rate was 86% in the clindamycin group and 83% in the piperacillin/tazobactam group (p>0.99).
Clindamycin plus Primaquine vs. Trimethoprim/ Sulfamethoxazole (TMP/SMZ) for Pneumocystis carinii pneumonia in patients with AIDS[18]	n=87	Multicenter, randomized, double-blind trial.	Patients received clindamycin 450 mg QID plus primaquine 15 mg of base/day or TMP/SMZ 240/1200 mg to 320/1600 mg QID plus primaquine placebo for 21 days. • Overall success rate was 76% in the clindamycin group vs. 79% in the TMP/SMZ group. • For patients with PaO2 <70 mm Hg, success rate was 74% in the clindamycin

			group and 76% in the TMP/SMZ group (95% CI, 2 ± 25%). • Adverse event rate was less in the clindamycin group (p=0.04).
Clindamycin plus Ciprofloxacin vs. Ceftriaxone and Doxycycline for pelvic inflammatory disease in outpatients[19]	n=131	Multicenter, prospective, double-blind trial.	Patients received clindamycin PO plus ciprofloxacin PO or ceftriaxone IM plus doxy cycline PO. • Clinical cure rate was 97% in the clindamycin group vs. 95% in the ceftriaxone group.
Colistin in critically ill patients with multi-drug resistant *P. aeruginosa* infection[20]	n=23	Non-controlled, consecutive enrollment.	Colistin IV was used as salvage therapy in patients receiving mechanical ventilation and had pneumonia (n=18) or intra-abdominal infection (n=5). • Received colistin for a median of 17 days. • Seven patients died during therapy. • Favorable clinical response was observed in 14 patients (61%). • Bacteremia was associated with clinical failure (p=0.02).
Colistin or Imipenem/Cilastatin for multi-drug resistant *Acinetobacter baumannii* ventilator-associated pneumonia[21]	n=35	Prospective, controlled, consecutive enrollment.	Patients were treated with colistin IV (n=21) 2.5 to 5 mg/kg/day divided TID or imipenem/cilastatin (n=14) 2 to 3 g/day when infection caused by imipenem-susceptible strains. • Clinical cure observed in 57% of patients in both groups. • In-hospital mortality rate was 61.9% in the colistin group vs. 64.2% in the imipenem group (p=ns). • Ventilator-associated pneumonia-related mortality rate was 38% in the colistin group vs. 35.7% in the imipenem group (p=ns). • Renal failure developed in 5 patients in the colistin group and 6 patients in the imipenem group (p>0.05).
Nebulized Colistin vs. Nebulized Tobramycin in cystic fibrosis[22]	n=115	Randomized trial.	Patients received either colistin or tobramycin nebulizer solution twice daily for 4 weeks. • Patients receiving colistin experienced a mean improvement in lung function of 0.37% (p=ns) vs. 6.7% with tobramycin (p=0.006). • Sputum density of *P. aeruginosa* was significantly decreased in both groups.
Colistin for acute respiratory exacerbations in adult patients with cystic fibrosis[23]	n=71	Randomized trial.	Patients received either colistin IV alone or with another anti-pseudomonal antibiotic for 12 days. • Forced expiratory volume in 1 second increased significantly in both groups (p<0.01). • Patients receiving dual therapy experienced a significant improvement in forced vital capacity (p<0.01). • Adverse neurological events occurred in 33 patients in the monotherapy group vs. 36 in the dual therapy group.
Daptomycin vs. Penicillinase-resistant	n=902	Pooled results of two multinational,	Patients received daptomycin 4 mg/kg IV QD, penicillinase-resistant penicillin 4 to 12 g IV QD, or

penicillins or Vancomycin for complicated skin and skin structure infections[24]		randomized, controlled trials.	vancomycin 1 g IV BID for 7 to 14 days. • Clinical success rate was 83.4% in the daptomycin group and 84.2% in the comparator groups (95% CI, -4 to 5.6%). • Of successful episodes, 63% in the daptomycin group and 33% in the comparator groups required 4 to 7 days of therapy (p<0.0001).
Linezolid vs. Teicoplanin for Gram-positive infections in intensive care population[25]	n=202	Prospective, randomized, double-blind, double-dummy trial.	Patients received linezolid IV 600 mg BID plus teicoplanin dummy or teicoplanin 400 mg IV BID for 3 doses then QD plus linezolid dummy. • Clinical success occurred in 78.9% of the linezolid group vs. 72.8% of the teicoplanin group. • Microbiological success occurred in 70% of the linezolid group vs. 66.2% of the teicoplanin group. • Clearance of methicillin-resistant *S. aureus* occurred in 51.1% of the linezolid cases vs. 18.6% of the teicoplanin cases (p=0.002).
Linezolid vs. Ampicillin/Sulbactam or Amoxicillin/Clavulanate for diabetic foot infections[26]	n=371	Open-label, multicenter, randomized trial.	Patients received therapy for 7 to 28 days. • Clinical cure rate was 81% with linezolid vs. 71% with comparators. • Clinical cure rate in patients with infected foot ulcers was 81% with linezolid vs. 68% with comparators (p=0.018). • Clinical cure rate in patients without osteomyelitis was 87% with linezolid and 72% with comparators (p=0.003). • Adverse drug events were significantly more common in the linezolid group.
Linezolid vs. Vancomycin for complicated skin and skin structure infections in children[27]	n=120	Randomized, controlled trial.	Patients received linezolid 10 mg/kg I V or PO every 8 hours or vancomycin 10 to 15 mg/kg IV every 6 to 14 hours. • Clinical cure rate was 93.2% with linezolid vs. 90% with vancomycin (p=0.594). • Fewer patients experienced adverse events with linezolid therapy (p=0.006).
Linezolid for vancomycin-resistant *E. faecium* in solid organ transplant patients [28]	n=85	Open-label, multicenter, compassionate-use trial.	• Clinical resolution occurred in 53 patients (62.4%). • Documented negative cultures post-therapy were obtained in 47 of these patients. • Mean duration of therapy for cured patients was 23.5 days. • Death occurred in 32 patients (37.6%). • Adverse reactions included thrombocytopenia, leukocytopenia, and increase in blood pressure.
Linezolid vs. Ceftriaxone/Cefpodoxime in patients hospitalized for pneumonia[29]	n=747	Open-label, multinational, randomized trial.	Patients received linezolid 600 mg IV/PO BID with optional aztreonam or a cephalosporin regimen (ceftriaxone 1 g IV BID followed by cefpodoxime 200 mg PO BID) and were assessed 12 to 28 days post-therapy. • Clinical cure rate was 83% with linezolid vs. 76.4% with cephalosporins (p=0.04).

			• *S. pneumoniae* eradication rates were similar in both groups (p=0.83). • Clinical cure rate in patients with *S. pneumoniae* was 93.1% with linezolid vs. 68.2% with cephalosporins (p=0.021). • Incidence of adverse events was 21.3% with linezolid vs. 11.2% with cephalosporins (p=0.0002).
Linezolid vs. Vancomycin for methicillin-resistant *S. aureus* infections[30]	n=460	Open-label, randomized, controlled trial.	Patients received linezolid 600 mg BID or vancomycin 1 g BID for 7 to 28 days. • Clinical cure rate was 73.2% with linezolid vs. 73.1% with vancomycin (p=0.99). • Microbiological success rate was 58.9% with linezolid vs. 63.2% with vancomycin (p=0.65). • Adverse event rates were similar (p=0.143).
Linezolid vs. Oxacillin/Dicloxacillin for complicated skin and soft tissue infections[31]	n=819	Multicenter, randomized, double-blind trial.	Patients received oxacillin 2 g IV every 6 hours followed by dicloxacillin 500 mg PO every 6 hours or linezolid 600 mg IV every 12 hours. • Clinical cure rate was 64.9% in the oxacillin/dicloxacillin group vs. 69.8% in the linezolid group (p=0.141).
Polymyxin B and Neomycin for selective gut decontamination in cardiopulmonary bypass patients [32]	n=78	Prospective, randomized, double-blind, placebo-controlled trial.	Patients received preoperative polymyxin B and neomycin PO or placebo or no medicine for 5 to 7 days. • Number of rectal swabs that grew aerobic Gram-negative bacteria was 27% in the active group vs. 93% in the placebo group (p<0.001). • Selective gut decontamination did not affect occurrence of perioperative endotoxemia or cytokine activation.
Trospectomycin vs. Ceftriaxone for uncomplicated gonorrhea[33]	n=100	Dual-center, randomized, comparative trial.	Patients received trospectomycin 250 mg IM or ceftriaxone 250 mg IM. • Among male patients, cure rate was 90% with trospectomycin and 100% with ceftriaxone. • Among female patients with cervical gonorrhea, cure rate was 100% with both trospectomycin and ceftriaxone. • Among female patients with pharyngeal gonorrhea, cure rate was 67% with trospectomycin and 100% with ceftriaxone.
Vancomycin for persistent fever in neutropenic cancer patients [34]	n=165	Prospective, randomized, double-blind trial.	Patients receiving piperacillin/tazobactam empiric therapy also received either vancomycin or placebo. • Defervescence occurred in 95% of the vancomycin group and 92% of the placebo group. • Difference in time to defervescence was not significant (p=0.75).
Vancomycin vs. Linezolid for resistant Gram-positive infections in children[35]	n=321	Randomized, controlled trial.	Patients from birth to age 12 years received vancomycin IV followed by appropriate oral therapy or linezolid IV followed by linezolid PO for 10 to 28 days. • Clinical cure rate was 74% with

			vancomycin and 79% with linezolid in intent-to-treat analysis (p=0.36). • Eradication rates for methicillin-resistant *S. aureus* were similar for both groups (p=0.89). • Patients receiving linezolid required fewer days of IV therapy (p<0.001) and experienced fewer adverse drug events (p<0.003).
Vancomycin vs. Metronidazole for recurrent episodes of *Clostridium difficile* disease[36]	n=163	Randomized, placebo-controlled trial.	Patients received oral vancomycin, metronidazole, or placebo. • Tapered and pulsed dose courses of vancomycin resulted in fewer recurrences (p=0.01 and p=0.02, respectively). • *C. difficile* was cleared in 89% of the vancomycin group vs. 59% of the metronidazole group (p<0.001).
Vancomycin or Teicoplanin plus Gentamicin vs. Cloxacillin plus Gentamicin for *S. aureus* infections in drug abusers[37]	n=31	Open-label, prospective, randomized trial.	Patients received vancomycin 500 mg IV QID, teicoplain 12 mg/kg IV QD, or cloxacillin 2 g IV every 4 hours. All patients received gentamicin 1.5 mg/kg TID. • Clinical failure occurred in 40% of the vancomycin group, 30% of the teicoplanin group, and none of the cloxacillin group (p=0.03 with vancomycin and p=0.09 with teicoplanin). • Therapeutic success was more frequent in the cloxacillin group (p=0.03). • No patient experienced microbiological failure. • Adverse effects occurred in 20% of the vancomycin group, 30% of the teicoplanin group, and none of the cloxacillin group.
Vancomycin vs. Linezolid for nosocomial pneumonia[38]	n=396	Multinational, randomized, double-blind, controlled trial.	Patients received vancomycin 1 g IV BID plus aztreonam or linezolid 600 mg BID plus aztreonam for 7 to 21 days. • Clinical cure rate was 68.1% with vancomycin and 66.4% with linezolid. • Microbiological success rate was 71.8% with vancomycin and 67.9% with linezolid.
Vancomycin/Heparin/ Ciprofloxacin flush solution for prevention of central line infections in immunocompromised children[39]	n=126	Multicenter, prospective, randomized, double-blind trial.	Patients received antibiotic flush solutions with vancomycin/heparin/ciprofloxacin (VHC), vancomycin/heparin (VH), or heparin alone for a total of 36 944 line days. • Infections occurred in 31 of the heparin group, 3 in the VH group, and 6 in the VHC group. • Time to infection was increased with VH (p=0.011) and VHC (p=0.036) compared to use of heparin alone. • Number of occlusions was significantly reduced with VHC (p=0.0005) but not with VH (p=0.37) compared to heparin alone.
Vancomycin vs. Cefazolin for prevention	n=265	Prospective, randomized,	Patients received vancomycin 1 g IV 12 hours before procedure, cefazolin 1 g IV 3 hours before

of postoperative peritonitis[40]		controlled trial.	procedure, or no antimicrobial medication for at least a week before procedure. • After 14 days, peritonitis developed in 1% of the vancomycin group and 12% of the control group (p=0.002) • After 14 days, peritonitis developed in 9% of the cefazolin group (p=0.68 compared to control).
Telithromycin vs. Cefuroxime for acute exacerbations of chronic bronchitis in adults[41]	n=282	Multicenter, randomized, double-blind, parallel-group trial.	Patients received telithromycin 800 mg QD for 5 days or cefuroxime 500 mg BID for 10 days. • Clinical cure rate was 86.4% with telithromycin vs. 83.1% with cefuroxime. • Eradication rate was 76% in the telithromycin group and 78.6% in the cefuroxime group.
Telithromycin vs. Clarithromycin for group A beta-hemolytic streptococcal tonsillitis/ pharyngitis[42]	n=463	Multicenter, randomized, double-blind, parallel-group trial.	Adolescent and adult patients received telithromycin 800 mg QD for 5 days or clarithromycin 250 mg BID for 10 days. • Clinical cure rate was 92.7% with telithromycin vs. 91.1% with clarithromycin (95% CI, -5.5 to 8.6%). • Bacterial eradication rate was 91.3% with telithromycin vs. 88.1% with clarithromycin (95% CI, -4.5 to 11%). • Diarrhea, nausea, and vomiting were more common with telithromcin (p=0.004, 0.01, and 0.001, respectively).

Additional Evidence

Dose Simplification: Carroll, et al. conducted a prospective, randomized clinical trial to determine efficacy of short-course (3 doses) versus long-course (15 doses) of clindamycin for prophylaxis of wound infection in patients with head and neck cancer undergoing reconstructive surgery.[43] In the 74 patients, incidence of wound infection and other complications was statistically insignificant between the two groups. Another study conducted by Livingston, et al. compared the efficacy of gentamicin and clindamycin given once daily versus every 8 hours (using the same drug formulations; no extended-release formulations are available) for treatment of postpartum endometritis.[44] Of the 110 patients, treatment success was achieved in 45 (82%) of the once-daily group compared to 38 (69%) of the three-times daily group (p=0.12).

Cohen, et al. conducted a prospective, randomized study in 121 patients to compare the efficacy of once-daily versus twice-daily dosing of vancomycin in hospitalized patients.[45] Favorable clinical response was achieved in 92.1% of the once-daily group compared to 94.2% of the twice-daily group (p=0.72).

Stable Therapy: Although literature is available to support clinical efficacy of agents in this class, facility-specific resistance rates must be considered when choosing appropriate anti-infective therapy. A study by McCollum et al. looked at switching from IV vancomycin to PO linezolid for the management of methicillin-resistant Staphylococcus species.[59] Of 177 patients treated with IV vancomycin, 103 (58%) were eligible for conversion to PO therapy with linezolid and 55 (31%) were eligible for early hospital discharge with continuation of oral therapy. Early discharge was associated with a length of stay decrease of 3.3 (2.9) days. No further literature was identified in Medlineor Ovid pertaining to continuation of antibiotics beyone hospitalization.

Impact on Physician Visits: Agents in this class are used for acute therapy. Use of appropriate therapy and conversion to oral therapy when appropriate may result in decreased length of hospital stay.

A study was conducted by Li, et al. to compare the effect of linezolid and vancomycin on length of hospital stay in patients with complicated skin and soft tissue infections.[46] Patients received linezolid IV followed by linezolid PO or vancomycin IV only for up to 4 weeks. Length of hospital stay was 9 days in the linezolid group versus 14 days in the vancomycin group (p=0.052).

IX. Conclusions

The drugs in this class are used primarily for hospitalized patients with serious infections, or are indicated for limited use in specific infectious diseases. Several agents have indications for resistant infections or for the second-line treatment of certain infections diseases (lincomycin and polymyxin b sulfate). These drugs would not routinely be used as first-line therapies on an outpatient basis. Generic formulations are available for over half of the drugs in this class. The only oral anti-infectives with no generic alternatives include lincomycin, vancomycin (pulvules), and linezolid.

Although there may be some clinical advantage to the drugs in this class in special needs/circumstances, there is not a role for these agents in general use. If needed, the oral therapies with no generic alternatives would be available with medical justification through the prior approval program, for their respective indications. Therefore, all brand products within the class reviewed are comparable to each other and to the generics in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand single entity miscellaneous antibacterial is recommended for preferred status.

Pharmacotherapy Review of the Miscellaneous Antibacterials
Combination Agents
AHFS 081228

I. Overview

There are two combination agents classified in the miscellaneous antibacterial class. No generic formulations are available for either drug. This review encompasses all dosage forms and strengths. Table 1 lists the drugs included in this review.

Table 1. Combination Miscellaneous Antibacterials in this Review

Generic Name	Formulation	Example Brand Name
Bismuth Subsalicylate, Metronidazole, Tetracycline	Oral tablet/capsule combination	Helidac
Dalfopristin/Quinupristin	Injection	Synercid

No generic formulations are available.

II. Evidence Based Medicine and Current Treatment Guidelines

As the single entity miscellaneous antibacterials review covered general guidelines for some resistant infections, the focus of this section will be on the treatment of *H. pylori*.

Helicobacter pylori (*H. pylori*) is a spiral-shaped bacterium found in the gastric mucous layer or adherent to the epithelial lining of the stomach.[47] The bacterium causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers. Since we now know that most ulcers are caused by *H. pylori*, appropriate antibiotic regimens can successfully eradicate the infection in most patients, with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers.

Approximately two-thirds of the world's population is infected with *H. pylori*. Infected persons have a 2-6 fold increased risk of developing gastric cancer and mucosal-associated-lymphoid-type (MALT) lymphoma compared with their uninfected counterparts.

Therapy for *H. pylori* consists of ten days to two weeks of one or two antibiotics, such as amoxicillin, tetracycline (not in children <12 years), metronidazole, or clarithromycin, plus either ranitidine bismuth citrate, bismuth subsalicylate, or a proton pump inhibitor. Acid suppression with an H-2 antagonist or proton pump inhibitor in conjunction with antibiotics helps alleviate ulcer-related symptoms, helps heal gastric mucosal inflammation, and may enhance efficacy of the antibiotics against *H. pylori* at the gastric mucosal surface.

Currently, eight *H. pylori* regimens are approved by the Food and Drug Administration (FDA). Antibiotic resistance and patient noncompliance are two major reasons for treatment failure. Eradication rates of the eight regimens range from 61% to 94% depending on the regimen used. Overall, triple therapy regimens have shown better eradication rates than dual therapy and longer length of treatment (14 days versus 10 days) results in better eradication rates. One study comparing dual versus triple H. pylori therapies showed retreatment rates were higher ($p<0.05$) for PPI based dual therapy than either bismuth or PPI based triple therapy.[58] Table 2 lists the FDA-approved treatment options for *H. pylori*.

Table 2. FDA-Approved Treatment Options[47]

Omeprazole 40mg QD + clarithromycin 500mg TID x 2 weeks, then omeprazole 20mg QD x 2 weeks
Ranitidine bismuth citrate 400mg BID + clarithromycin 500mg TID x 2 weeks, then ranitidine bismuth citrate 400mg BID x 2 weeks.
Bismuth subsalicylate (Pepto Bismol) 525mg QID + metronidazole 250mg QID + tetracycline 500mg QID x 2 weeks + H2 receptor antagonist therapy as directed x 4 weeks.
Lansoprazole 30mg BID + amoxicillin 1g BID + clarithromycin 500mg TID x 10 days
Lansoprazole 30mg TID + amoxicillin 1g TID x 2 weeks**
Ranitidine bismuth citrate 400mg BID + clarithromycin 500mg BID x 2 weeks, then ranitidine bismuth citrate 400mg BID x 2 weeks
Omeprazole 20mg BID + clarithromycin 500mg BID + amoxicillin 1g BID x 10 days
Lansoprazole 30mg Bid + clarithromycin 500mg BID + amoxicillin 1g BID x 10 days

**This dual therapy regimen has restrictive labeling. It is indicated for patients who are either allergic or intolerant to clarithromycin or for infections with known or suspected resistance to clarithromycin.

Recent studies have shown an association between long-term infection with *H. pylori* development of gastric cancer.[47] Gastric cancer is the second most common cancer worldwide and is most common in countries such as Colombia and China, where *H. pylori* infects over half of the population in early childhood. In the United States, where *H. pylori* is less common in young people, gastric cancer rates have decreased since the 1930s.

III. Indications of the Combination Miscellaneous Antibacterials

Table 3 lists the FDA-approved indications for the drugs in this review.

Table 3. FDA-Approved Indications of the Combination Miscellaneous Antibacterials[5-7]

Drug	Indication
Bismuth Subsalicylate, Metronidazole, Tetracycline	The components in combination with an H-2 antagonist, are indicated for the eradication of *H. pylori* for the treatment of patients with *H. pylori* infection and duodenal ulcer disease.
Dalfopristin/Quinupristin	**Life-threatening infections:** Treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. **Complicated skin and skin structure infections:** Caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*.

IV. Pharmacokinetics of the Combination Miscellaneous Antibacterials

Upon oral administration, bismuth subsalicylate is completely hydrolyzed in the gastrointestinal tract to bismuth and salicylic acid. The relative contribution of systemic versus local antimicrobial activity against *H. pylori* for agents used in eradication therapy has not been established. The pharmacokinetics of each are described below. Table 4 lists the common pharmacokinetic parameters with the two agents in this class.

Table 4. Pharmacokinetic Parameters of the Combination Miscellaneous Antibacterials[5-7]

Drug	Mechanism of Action	Bio-availability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Bismuth, Salicylic acid, Metronidazole, Tetracycline	Agent specific	<1% >80% Well absorb. Readily absorbed	>90% 90% <20% Varies	- Yes Yes Yes	- - - -	Urinary/biliary Urine Urine Urine/feces	21-72 days 2-5 hours 8 hours -
Dalfopristin / Quinupristin	Inhibition of late and early phases of protein synthesis, by binding at different sites on the 50S subunit of the bacterial ribosome.	-	Moderate	Non-enzymatic reactions, not dependent on CYP P450	Yes	Primarily fecal excretion; urinary excretion for 15% of quinupristin and 19% of dalfopristin dose.	Elimination: 0.7 and 0.85 hours, respectively

V. Drug Interactions of the Combination Miscellaneous Antibacterials

Quinupristin/Dalfopristin

Quinupristin/dalfopristin is a major inhibitor of the activity of cytochrome P450 3A4 isoenzyme.[5-7] Therefore, it is reasonable to expect that concomitant administration of it and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of drugs that could increase or prolong their therapeutic effect or increase adverse events. The drug can interfere with the metabolism of other drug products that are associated with QTc prolongation. The following selected drugs have been predicted to have plasma concentrations increased by quinupristin/dalfopristin[1]:

1. Anti-HIV (NNRTIs and protease inhibitors): Delavirdine, nevirapine, indinavir, ritonavir
2. Antineoplastic agents: Vinca alkaloids (e.g., vinblastine), docetaxel, paclitaxel
3. Benzodiazepines: Midazolam, diazepam
4. Calcium channel blockers: Dihydropyridines(e.g., nifedipine), verapamil, diltiazem
5. Cholesterol-lowering agents: HMG-CoA reductase inhibitors
6. GI motility agents: Cisapride
7. Immunosuppressive agents: Cyclosporine, tacrolimus
8. Steroids: Methylprednisolone
9. Other: Carbamazepine, quinidine, lidocaine, disopyramide

[1]This list of drugs is not all inclusive.

Additionally, digoxin and quinupristin/dalfopristin have a potential pharmacokinetic interaction based on inhibition of GI metabolism via *Eubacterium lentum* eradication. Quinupristin/dalfopristin has also been shown to increase the AUC of cyclosporine, a 30% increase in the Cmax, and a 77% increase in the half-life of cyclosporine.[7] Therapeutic level monitoring of cyclosporine should be used when patients are concomitantly receiving quinupristin/dalfopristin.

Bismuth Subsalicylate, Metronidazole, Tetracycline
Individual components of this combination have the potential to interact with anticoagulants.[5-7] Tetracycline has been shown to depress plasma prothrombin activity. Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Salicylates may cause an increased risk of bleeding when administered with anticoagulant therapy. Monitoring anticoagulant therapy with appropriate adjustment of the anticoagulant dosage may be warranted if concurrent therapy is instituted.

Caution is advised in the administration of bismuth subsalicylate to patients taking medication for diabetes (possible enhanced hypoglycemic effect when given with salicylates) or patients taking aspirin, probenecid, or sulfinpyrazone.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium; preparations containing iron, zinc, or sodium bicarbonate; or milk or daily products.

Since bacteriostatic drugs, such as the tetracycline class of antibiotics, may interfere with the bactericidal action of penicillin, it is not advisable to administer these drugs concomitantly.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective. Patients should be advised to use a different or additional form of contraception. Breakthrough bleeding has been reported. Women who become pregnant while on the Helidac therapy should be advised to notify their prescriber immediately.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. Administration of metronidazole with drugs that induce microsomal liver enzymes, such as phenytoin or Phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels. Impaired clearance of phenytoin has also been reported.

In patients stabilized on high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine should be obtained several days after beginning metronidazole to detect any increases that may precede clinical lithium intoxication.

Alcoholic beverages should not be consumed during metronidazole therapy for at least 1 day afterward because of abdominal cramps, nausea, vomiting, headaches, and flushing.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

VI. Adverse Events of the Combination Miscellaneous Antibacterials

In trials, approximately 33% of patients discontinued therapy with quinupristin/dalfopristin because of adverse events.[7] More specifically, the discontinuation rate because of adverse events assessed by the investigator as possibly or probably related to quinupristin/dalfopristin therapy was approximately 5%.

Table 5. Common Adverse Events (%) Reported for the Combination Miscellaneous Antibacterials[5-7]

Adverse Event	Bismuth Subsalicylate, Metronidazole, Tetracycline*	Quinupristin/Dalfopristin
Body as a Whole		
Malaise		
Pain	1.1	0.5
Cardiovascular		
Edema		< 1%
Hypotension		
Hypertension		
Digestive System		
Abdominal Pain	6.8	< 1%
Nausea / Vomiting	12 (nausea)/1.5 (vomiting)	0.9/0.5
Diarrhea	6.8	> 1%
Epigastric distress	1.5 (dyspepsia)	< 1%
Appetite decrease	1.5	
Melena	3.0	
Constipation	1.9	< 1%
Stool Abnormality	1.1	
Duodenal Ulcer	1.1	
Flatulence	1.1	
GI Hemorrhage	1.1	
Anal discomfort	1.1	
Central Nervous System		
Dizziness/Vertigo	1.5	< 1%
Fatigue		
Fever		< 1%
Headache	1.5	> 1%
Meningeal Signs		
Confusion		< 1%
Drowsiness		
Insomnia	1.1	< 1%
Paresthehsia	1.1	< 1%
Hepatic		
Abnormal LFTs (incr.)		> 0.1%
Hyperbilirubinemia (>5 x ULN)		25%
Hepatic failure		
Skin and Appendages		
Rash		1.0
Pruritus		0.5
Hematologic		
Neutropenia		
Agranulocytosis		
Leukopenia		
Thrombocytopenia		
Renal		
Abnormal kidney fxn		
Acute kidney failure		
Other		
Inflammation/pain at inj. site		> 1%
Discolored Tongue	1.5	
Upper Respiratory Infection	2.3	
Sinusitis	1.1	
Taste perversion	1.1	
Venous		9.2
Non-venous		9.6
Gout		< 1%

* Common adverse events in = 1% of patients reported in clinical trials when all three components were given concomitantly.

VII. Dosage and Administration of the Combination Miscellaneous Antibacterials

Table 6. Dosing for the Combination Miscellaneous Antibacterials[5-7]

Drug	Availability	Dosing and Administration
Bismuth, Salicylic acid, Metronidazole, Tetracycline	Tablets: 262.4mg bismuth subsalicylate, 250mg metronidazole Capsule: 500mg tetracycline	**Adults:** Take 525mg bismuth subsalicylate, 250mg metronidazole and 500mg tetracycline plus an H_2 antagonist 4 times daily at meals and at bedtime for 14 days. Chew and swallow the bismuth subsalicylate tablets. Swallow the metronidazole tablet and tetracycline capsule whole with a full glass of water (8 ounces). Take concomitantly with prescribed H_2 antagonist therapy as directed. Ingestion of adequate amounts of fluid, particularly with the bedtime dose of tetracycline HCl, is recommended to reduce the risk of esophageal irritation and ulceration. Missed doses can be made up by continuing the normal dosing schedule until the medication is gone. Do not take double doses. If more than four doses are missed, contact the physician. Note: The manufacturer recommends patients who experience treatment failures with this drug combination be retreated with a regimen that does not contain metronidazole.
Dalfopristin / Quinupristin	Injection, lyophilized: 500mg (150mg quinupristin; 350mg dalfopristin)/10 ml	Indication: Vancomycin-resistant *Enterococcus faecium* — Dose: 7.5mg/kg q8hr Indication: Complicated skin and structure infection — Dose: 7.5mg/kg q12hr The minimum recommended treatment duration for complicated skin and skin structure infections is 7 days. For vancomycin-resistant *E. faecium* infection, base treatment duration on the site and severity of the infection.

Special Dosing Considerations

Table 7. Special Dosing Considerations for the Combination Miscellaneous Antibacterials[5-7]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed?
Bismuth, Salicylic acid, Metronidazole, Tetracycline	Is contraindicated in patients with renal or hepatic impairment.		Is contraindicated in pediatric patients.	Is contraindicated in pregnant or nursing women.	Bismuth subsalicylate tablets should be chewed and swallowed; metronidazole and tetracycline should be swallowed whole.
Dalfopristin / quinupristin	No	Pharmacokinetic data in patients with hepatic cirrhosis (Child Pugh A or B) suggest that dosage reduction may be necessary, but exact recommendations cannot be made at this time.	Safety and efficacy have not been established in children younger than 16 years of age.	B	N/A, injection only

VIII. Comparative Efficacy of the Combination Miscellaneous Antibacterials

Table 8. Outcomes Evidence for the Combination Miscellaneous Antibacterials

Study	Sample	Design	Results
Quinupristin/Dalfopristin (Q/D) vs. Linezolid for vancomycin-resistant *E. faecium* infection in cancer patients[48]	n=40	Randomized trial	Patients received Q/D 7.5 mg/kg TID or linezolid 600 mg BID. • Comparable clinical response in both groups (p=0.6). • Myalgias and/or arthralgias occurred more often in the Q/D group (p=0.03). • Thrombocytopenia occurred more often in the linezolid group (p=0.02).
Quinupristin/Dalfopristin (Q/D) vs. Vancomycin for Gram-positive nosocomial pneumonia[49]	n=171	Open-label, multinational, randomized, comparative trial	Patients received QD 7.5 mg/kg TID or vancomycin 1 g BID. Aztreonam and tobramycin were optional in both groups. • Clinical success was achieved in 56.3% of the Q/D group vs. 58.3% of the vancomycin group (95% CI, -16.8 to 12.8%). • Adverse event rates were similar in both groups (p=0.12).
Quinupristin/Dalfopristin for methicillin-resistant *S. aureus* infections[50]	n=90	Multinational, consecutive enrollment	Patients received 7.5 mg/kg IV TID and assessed 7 to 21 days post-therapy. • Overall success rate was 71.1%. • Common adverse events were arthralgias (10.8%), myalgias (8.6%), and nausea (8.6%).
Triple (PPI, clarithromycin, and amoxicillin or an imidazole) vs. quadruple (PPI, tetracycline, metronidazole, and bismuth) therapy for *H. pylori*[51]	Four studies met inclusion criteria	Meta-analysis	Due to decreasing efficacy of triple therapy for *H. pylori* from antibiotic resistance, a meta-analysis was performed to compare triple vs. quadruple for first-line therapy: • Eradication rates with quadruple therapy were slightly higher in both the intention-to-treat (81% vs. 78%; odds ratio, 0.83; 95% confidence interval, 0.61-1.14) and per protocol (88% vs. 85%; odds ratio, 0.81; 95% confidence interval, 0.55-1.20) analysis, although the differences were not statistically significant. • Nor were there significant differences in compliance or adverse effects between the therapies. • Summary: Triple and quadruple therapies seem to be roughly equivalent in terms of effectiveness, compliance and side-effects profile when administered as first-line treatment for H. pylori infection.
Ranitidine-bismuth citrate, tetracycline, and metronidazole x seven days, followed by omeprazole, clarithromycin, and amoxicillin for seven days[52]	n=136	-	In order to evaluate the efficacy of a strategy combining ranitidine-bismuth citrate triple therapy followed by a proton pump inhibitor triple therapy for *H. pylori* eradication: • The efficacy of the treatment was evaluated by histology or the urea breath test. • Cure rates were 109/136 patients [80.2%; 95% confidence interval (CI), 72-86%] by intention to treat and 109/127 (85.8%; 95% CI, 78-91%) per protocol. • Fifteen of the patients with treatment failure

			received second-line treatment. • Cure rates for the strategy as a whole were 119/136 (87.5%; 95% CI, 81-92%) by intention to treat and 119/123 (96.8%; 95% CI, 92-99%) per protocol. • Summary: This strategy achieves good eradication rates. As the first-line therapy avoids the use of clarithromycin, it could be useful in areas where high resistance to this antibiotic lead to poor results with triple therapy.
Ranitidine bismuth citrate, tetracycline, and metronidazole vs. ranitidine bismuth citrate and azithromycin in the eradication of *H. pylori* in patients resistant to PPI based triple therapy[53]	n=52	Randomized, comparative study	Ten to twenty percent of patients remain infected despite treatment with proton pump inhibitors (PPIs), amoxicillin, and clarithromycin. This evaluation included patients with previous triple therapy with PPI, clarithromycin, and amoxicillin, for 14 days and were found to be resistant to this therapy. These patients were then randomized to ranitidine bismuth citrate, tetracycline, and metronidazole for 14 days (RbTM), or ranitidine bismuth citrate (14 days) and azithromycin for 7 days (RbA). • A total of 52 patients, 32 females and 20 males with a mean age of 49+/-12 years, were included in the study. • Eradication was achieved in 15 (28%) out of 52 patients in total. • There was a significant difference between RbA and RbTM groups (p=0.01). In fact, H. pylori was eradicated in 3 (12%) out of 25 patients in the RbA group, whereas it was eradicated in 12 (44.4%) out of 27 patients in the RbTM group. • Symptom scores significantly improved in both groups after the treatment, though there was not a significant difference between the groups (p=0.705). • Summary: Triple therapy including azithromycin does not seem to be a good choice in cases resistant to the first line therapies; however, a similarly lower rate of eradication was achieved with the quadruple therapy proposed (PPI, bismuth, tetracycline, and metronidazole). Therefore, different treatment schemes should be applied in resistant patients, and further studies are needed as well.
Quadruple therapy vs. high dose dual therapy for *H. pylori* resistant to metronidazole and clarithromycin[54]	n=84	Prospective, randomized study	In evaluating the efficacy of high dose dual therapy and quadruple therapy as salvage treatments for eradication of *H. pylori* infections resistant to both metronidazole and clarithromycin. Patients with at least one treatment failure and infected with *H. pylori* resistant to metronidazole and clarithromycin, were randomized to receive either 1) omeprazole and amoxicillin or 2) omeprazole, bismuth citrate, metronidazole, and tetracycline, both regimens for 14 days. • Cure of H. pylori infection was achieved in 31

			patients after dual therapy and in 35 patients after quadruple therapy (per protocol: 83.8% (95% CI, 67.9-93.8) and 92.1% (95% CI, 78.6-98.3), respectively (p=0.71); intention to treat: 75.6% (95% CI: 59.7-87.6) and 81.4% (95% CI: 66.6-91.6), respectively (p=0.60)). • Summary: Both high-dose dual therapy and quadruple therapy are effective in curing H. pylori infection resistant to both metronidazole and clarithromycin in patients who experienced previous treatment failures.

Additional Evidence

Dose Simplification: A study of 125 patients with peptic ulcer disease or dyspepsia whose clinicians prescribed bismuth subsalicylate, metronidazole, and tetracycline (BMT) for the treatment of *H. pylori*, for 14 days, were randomized to a control group or to the enhanced compliance program (ECP).[55] The ECP group received medication counseling (written and oral) from a pharmacist, along with a medication calendar and a mini pillbox, as well as a follow-up telephone call after initiation of therapy.

There was no statistically significant difference between the 2 groups in the number of patients taking more than 60% of the medications (89% of the control group vs. 95% of the ECP group; P>.30). However, there was a statistically significant difference in the number of patients taking more than 90% of the medications (67% of the control group vs. 89% of the ECP group; P<.01). An intention-to-treat analysis confirmed these results. The most frequently reported adverse effect was gastrointestinal intolerance. Other factors reported to affect compliance included the frequency of dosing and the number of pills. These findings suggest that although adverse effects were common, most patients were able to complete 60% or more of the 2-week regimen. An ECP further improved the percentage of medications taken.

Additionally, *H. pylori* combination treatments are available that offer twice daily dosing frequencies. These agents are not being evaluated as part of this review.

With quinupristin/dalfopristin, administration is typically given during hospitalization, for serious infections where other antibiotics may not be alternatives. Dose simplification would not be applicable in these situations.

Stable Therapy: Limited data is available in the literature on changing from one *H. pylori* therapy to another. Studies were presented in table 8 that looked at *H. pylori* treatment due to resistant infections. A change in therapy is necessary in most infectious diseases, due to treatment failure and/or resistance.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical data pertinent to physician visits with quinupristin/dalfopristin or with bismuth subsalicylate, tetracycline, and metronidazole.

IX. Conclusion

The two combination miscellaneous antibacterials in this class are used for very different infections. Quinupristin/dalfopristin is only available as an injection, and is for life-threatening and complicated skin and skin structure infections. There is not a role for this anti-infective agent in general use. Should treatment with this agent be necessary for long-term care or other special needs/circumstances, the drug would be available through establishment of medical necessity, through the prior authorization program.

The bismuth subsalicylate, metronidazole, and tetracycline combination product, for eradication of *H. pylori*, is not available as a generic formulation combination product. However, each ingredient within this combination is available in a generic formulation and/or over-the-counter (H-2 antagonist for use with this combination product, and bismuth subsalicylate). This regimen is one of eight treatments recommended by the CDC for *H. pylori* eradication. Use of *H. pylori* treatment regimens should be monitored to ensure proper use based on positive diagnosis of the organism.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products within the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendation

No brand combination miscellaneous antibacterial is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Antimycobacterials-
Single Entity Agents
AHFS 081600, 081604, 081692
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I. Overview

Mycobacteria are unusual bacteria with a waxy cell wall structure, making them difficult to stain and for antimycobacterials to penetrate their cell walls. Mycobacteria are very slow growing, also hindering antimycobacterial activity. Drug resistance occurs primarily due to point mutations in the bacterial chromosome. Multiple combination antimycobacterials are often used to combat drug resistance. Antimycobacterials often have unpleasant adverse drug effects that can lead to poor compliance and contribute to the emergence of resistant strains. Mycobacteria are the causative organisms for tuberculosis and leprosy.

Tuberculosis: Tuberculosis (TB) is a common disease transmitted by inhaling airborne bacilli, *Mycobacterium tuberculosis*, from an active infective TB patient. TB has emerged as the single leading cause of death from any single infectious agent.[1] It is estimated that one-third of the world's population is latently infected.[1, 2] The United States has undergone TB resurgence due to many factors, including the immunodeficiency virus (HIV) pandemic and increases in the number of cases reported with foreign born people. Reduction in cell-mediated immunity associated with HIV infection is considered to be the greatest risk factor for the activation of latent TB. Increased prevalence of multi-drug resistant tuberculosis (MDR-TB) is a serious concern in the United States, leading to outbreaks especially in HIV infected people.

After being transmitted, *M. tuberculosis* multiplies in the alveolus and is carried by macrophages, lymphatics and blood to various sites (e.g. Lung pleura, brain, kidney, and bone). Latent tuberculosis infection (LTBI) is asymptomatic and noninfectious, but is usually detected by a positive skin test. Active TB occurs in 10% of infected individuals without preventive therapy.[3] The likelihood of active infection increases with immunosuppression, and is highest for all individuals within two years after infection. Eighty-five percent of cases are pulmonary, which is infectious.[3] Primary TB is disease resulting from the initial pulmonary infection that the immune system is unable to control. Recrudescent TB is active disease occurring after a latent asymptomatic period.

Leprosy:[4] Leprosy, also known as Hansen's disease, is a chronic granulomatous infection caused by *Mycobacterium leprae* that usually infects skin, mucous membranes, and peripheral nerves. *M. leprae* multiplies very slowly and has never been grown in a bacteriologic media or cell culture. In 2002, 763,917 new cases were detected worldwide, with 96 cases in the United States. Prevalence has remained stable in the United States. The majority of cases are believed to be in Brazil, Madagascar, Mozambique, Tanzania, and Nepal. Worldwide, one to two million people are permanently disabled from leprosy. Persons receiving antibiotic treatment or having completed treatment are considered free of active infections. *M. leprae* may be spread from person to person in respiratory droplets, even though the exact mode of transmission is unknown. Close contact with patients with untreated active predominantly multibacillary disease, and living in countries with highly endemic disease, are risk factors for infection.

Symptoms include hypopigmented skin macules, symmetric skin lesions, nodules, plaque, thickened dermis, neuritic pain, muscle atrophy, facial nerve damage, nasal congestions, and epistaxis. Patients are classified as Paucibacillary (mild) or Multibacillary disease.

This review encompasses all Antimycobacterial dosage forms and strengths.

Table 1. Single Entity Antimycobacterials in this Review[5]

Generic Name	Formulation	Example Brand Name (s)
Isoniazid	Oral Tablets*, Elixir, Injection	Nydrazid (injection)
Capreomycin sulfate	Powder for Injection	Capastat
Rifabutin	Oral Capsules	Mycobutin
Aminosalicyclic acid	Oral Granules	Paser
Rifapentine	Oral Tablets	Priftin
Pyrazinamide	Oral Tablets*	-
Rifampin	Oral Capsules, Powder for Injection	Rifadin, Rimactane*
Cycloserine	Oral Capsules	Seromycin
Ethionamide	Oral Tablets	Trecator-SC
Dapsone	Oral Tablets	-
Clofazimine#	Oral Capsules	Lamprene
Ethambutol	Oral Tablets	Myambutol*

*Generic Available.
#Only Available via National Hansen's disease Program

II. Evidence Based Medicine and Current Treatment Guidelines

Tuberculosis:[6]
American Thoracic Society, Centers for Disease Control and Prevention (CDC), and Disease Society of America's guidelines are considered to be the standard of practice for TB treatment. Overall, treatment goals are to cure the individual patient and to minimize the transmission of *Mycobacterium tuberculosis* to others. The successful treatment of TB has benefits for the individual patient and the community. Prescribing physician responsibility for treatment completion is a fundamental treatment principle. Patient-centered care should always include an adherence plan that emphasizes directly observed therapy (DOT), in which patients are observed to ingest each dose of anti-TB medications to maximize the likelihood of therapy completion.

Anti-TB drugs have three areas of activity: bactericidal, sterilizing, and drug resistance prevention. Isoniazid is the most potent bactericidal agent, and rifampin has some bactericidal activity. Rifampin and pyrazinamide are the most potent sterilizing drugs. The recommended treatment regimens for drug susceptible organisms are divided into two phases. Rapidly multiplying *M. tuberculosis* is killed during the initial phase of two months. Sterilizing drugs kill the intermittently dividing *M. tuberculosis* during the continuation phase of four or seven months. Multiple drugs are used because of possible drug resistance.

First line medications include isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, and ethambutol. Second line medications include cycloserine and ethionamide.

First line anti-TB medications should be administered together and dose splitting should be avoided. Combination medications may be administered more easily than single medications and aid in patient compliance, thereby possibly reducing acquired resistance. First line anti-TB medications should not be discontinued for minor side effects such as gastrointestinal upset. Medications may be taken with food to decrease gastrointestinal upset, although food may delay or moderately decrease medication absorption. Drug induced hepatitis is the most severe common adverse effect.

Table 2. Drug Regimens for Culture Positive Pulmonary Tuberculosis Caused by Drug Susceptible Organisms [6]

Initial Phase			Continuation Phase			Range of Total doses (minimal duration)	Rating* (evidence)#	
Regimen	Drugs	Interval & doses^ (minimal duration)	Regimen	Drugs	Interval & doses ^ς (minimal duration)		HIV-	HIV+
1	IHN RIF PZA EMB	7 d /wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/ RIF	7 d/wk for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182-130 (26 wk)	A (I)	A (II)
			1b	INH/ RIF	2 d/wk for 36 doses (18 week)	92-76 (26 wk)	A (I)	A (II)•
			1c‡	INH/ RPT	1 d /wk for 18 doses	74-58 (26 wk)	B (I)	E (I)
2	IHN RIF PZA EMB	7 d/wk for 14 doses (2 wk), then 2 d/wk for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)¶, then 2 d/wk for 12 doses (6 wk)	2a	INH/ RIF	2 d/wk for 36 doses (18 wk)	62-58 (26 wk)	A (II)	B (II)•
			2b‡	INH/ RPT	1 d/wk fro 18 doses (18 wk)	44-40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	3 d/wk for 24 doses (8 wk)	3a	INH/ RIF	3 d/wk for 54 doses (26 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/ RIF	7 d/wk for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273-195 (39 wk)	C (I)	C (II)
			4b	IHN/ RIF	2 d/wk for 62 doses (31 wk)	118-102 (39 wk)	C (I)	C (II)

Drug Abbreviations: EMB=Ethambutol; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; RPT=rifapentine

* Definitions of evidence ratings: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; E= should never be given

Definition of evidence ratings: I=randomized clinical trial; II=data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion

^When DOT is used, drugs may be given 5 d/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice.

ς Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 wk), either 217 doses (daily) or 62 doses (2 d/wk) continuation phase.

¶ Five-day-a-week administration is always given by DOT. Rating for 5 d/wk regimens is A (III)

• Not recommended for HIV-infected patients with CD4+ cells counts <100 cells/ul.

‡Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

III. Comparative Indications of the Single Entity Antimycobacterials

Table 3. FDA-Approved Indications for the Single Entity Antimycobacterials[5]

Drug	Leprosy	Tuberculosis	Prevention of Mycobacterium avium complex (MAC)	Multi-drug Resistant tuberculosis	Dermatitis herpetiformis	Acute UTI
Isoniazid		**X**				
Capreomycin sulfate		**X**				
Rifabutin			**X**			
Aminosalicyclic acid		**X**		**X**		
Rifapentine		**X**				
Pyrazinamide		**X**				
Rifampin		**X**				
Cycloserine		**X**				**X**
Ethionamide		**X**				
Dapsone	**X**				**X**	
Clofazimine	**X**					
Ethambutol		**X**				

IV. Pharmacokinetic Parameters

Table 4. Pharmacokinetic Parameters of the Single Entity Antimycobacterials[5]

Drug	Mechanism of Action	Bioavailability	Protein Binding	Metabolism	Active Metabolites
Isoniazid	Inhibits mycolic acids synthesis	Rapid and complete absorption	10-15%	Hepatic Acetylation and dehydrazination	N-acetylisoniazid
Capreomycin sulfate	Mechanism is unknown but is considered to be a cyclic polypeptide antimicrobial.	N/A	-	Excreted unaltered	-
Rifabutin	Suppress RNA synthesis by inhibiting DNA-dependent RNA polymerase	Readily Absorbed (53%); Absolute: HIV 20%	85%	Hepatic	31-hydroxy and 25-O-desacetyl rifabutin
Aminosalicyclic acid	PABA competitive antagonist	Readily Absorbed (<90%)	50-60%	Hepatic acetylation	
Rifapentine	Suppress RNA synthesis by inhibiting DNA-dependent RNA polymerase	Food increases AUC and Cmax by 43% and 44% respectively to around 70%	93-97%	Hepatic hydrolysis	25-desacetyl rifapentine
Pyrazinamide	Exact mechanism not known, but lowers pH by conversion to pyrazine acid	Well absorbed	50%	Hepatic hydroxylation	Pyrazinoic acid
Rifampin	Suppress RNA synthesis by inhibiting DNA-dependent RNA polymerase	N/A	80%	Hepatic deacetylation	Desacetyl-rifampicin
Cycloserine	Inhibits bacterial cell wall synthesis by competing with D-alanine	70-90%		Hepatic	Unknown substances
Ethionamide	Inhibits peptide synthesis	Completely absorbed	10-30%	Hepatic	Ethionamide-sulfoxide
Dapsone	PABA competitive antagonist	Well absorbed, Nearly 100%	70-90%	Hepatic acetylation	Monoacetyl-dapsone
Clofazimine	Inhibits growth by viding to mycobacterial DNA	Variable absorption (45-62%)	Highly lipophilic	Hepatic	-
Ethambutol	Interferes with RNA synthesis	Approx. 80%	20-30%	Hepatic	-

V. Drug Interactions

Table 5 describes the level 1 and 2 (most significant) drug interactions with the single entity antimycobacterials.

Table 5. Significant Drug Interactions of the Single Entity Antimycobacterials[7]

Drug	Significance	Interaction	Mechanism
Isoniazid	Level 2 (delayed, moderate, suspected)	Isoniazid and chlorzoxazone	Isoniazid may inhibit hepatic metabolism (CYP2E1) elevating plasma concentrations, increasing the therapeutic and adverse effects.
Isoniazid	Level 2 (rapid, moderate, suspected)	Isoniazid and enflurane	Rapid acetylation of isoniazid produces high concentration of hydrazine that facilitates deflurination of enflurane. High output renal failure may occur due to nephrotoxic concentrations in rapid isoniazid acetylators.
Isoniazid	Level 2 (delayed, moderate, established)	Isoniazid and hydantoins	Isoniazid inhibits the hepatic microsomal enzyme metabolism of hydantoins. Serum hydantoins levels may be increased resulting in increased pharmacologic and toxic effects of hydantoins.
Isoniazid	Level 1 (delayed, major, probable)	Isoniazid and rifampin	Possible alternation in Isoniazid metabolism. Hepatotoxicity may occur at a higher rate than with either agent alone.
Capreomycin	Level 2 (rapid, moderate, probable)	Capreomycin and nondepolarizing muscle relaxants	Capreomycin may affect pre-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants resulting in enhanced neuromuscular blockage.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and amprenavir	Amprenavir may decrease rifamycins metabolism while rifamycins increase amprenavir metabolism.
Rifamycins‡	Level 2 (delayed, moderate, established)	Rifamycins and anticoagulants	Increased hepatic metabolism of anticoagulants resulting in decreased anticoagulation actions.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and azole antifungals	Rifamycins may induce metabolism of azole antifungals while ketoconazole may interfere with rifamycin absorption and itraconazole may inhibit rifamycin metabolism. Plasma levels of azole antifungals may be decrease; ketoconazole may decrease rifamycin levels; itraconazole may increase rifamycins levels.
Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and beta-blockers, quinine derivatives, sulfonylureas, and propafenone	Possibly due to increased hepatic metabolism induced by rifamycins resulting in reduced pharmacologic effects.
Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and buspirone	Induction of first pass metabolism of buspirone by rifamycins resulting in decreased buspirone plasma concentrations and pharmacologic effects.
Rifamycins‡	Level 1 (delayed, major, established)	Rifamycins and corticosteroids, and theophylline	Rifamycins may increase hepatic metabolism resulting in decreased effects.
Rifamycins‡	Level 1 (delayed, major, probable)	Rifamycins and cyclosporine	Rifamycins increase hepatic and intestinal metabolism of cyclosporine resulting in reduced immunosuppressive effects for cyclosporine.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and estrogens	Rifamycins induce hepatic drug metabolizing enzymes of estrogens increasing 4-fold in vitro and in vivo. AUC and half-life also are decreased. Rifamycins may impair the effectiveness of estrogens; menstrual disturbances have been noted.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and haloperidol, HMG-CoA Reductase Inhibitors, hydantoins, delavirdine, indinavir, lamotrigine, doxycycline, benzodiazepines, meglitnides, nelfinavir, ondansetron, ritonavir, saquinavir, tricyclic antidepressants, tamoxifen, and toremifene	Metabolism induction decreasing plasma concentrations and effectiveness.

Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and macrolide antibiotics	Rifamycins' metabolism may be inhibited while macrolide metabolism may be increased. The antimicrobial effects of the macrolide may be deceased while the frequency of adverse GI reactions and adverse effects of rifamycins may be increased.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and morphine	Unknown mechanism. Decreased morphine analgesic effects.
Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and nifedipine	Possibly caused by increased gut wall metabolism (cytochrome P450 3A4) induced by rifamycins resulting in reduced therapeutic effects.
Rifamycins‡	Level 1 (delayed, major, probable)	Rifamycins and tacrolimus	Possible hepatic and intestinal metabolism (CYP3A4) induced by rifamycins. The immunosuppressive effects of tacrolimus may be reduced as early as 2 days after starting rifamycins.
Rifamycins‡	Level 1 (delayed, major, suspected)	Rifamycins and voriconazole	Rifamycins increase the metabolism of voriconazole, and voriconazole inhibits the metabolism of rifamycins. Voriconazole plasma concentrations may be reduced, decreasing the therapeutic effect and Rifamycins' plasma levels may be elevated increasing the risk of side effects.

‡ Rifamycins include rifabutin, rifapentine, and rifampin.

Other Interactions:

- Isoniazid and acetaminophen = Increased hepatotoxicity
- Isoniazid and anticoagulants = Enhanced anticoagulant activity
- Isoniazid and benzodiazepines = Enhanced benzodiazepine effect
- Isoniazid or ethionamide, and cycloserine = Increased cycloserine CNS side effects
- Isoniazid and disulfiram = Acute behavioral and coordination changes
- Isoniazid and aluminum salts = Decreased isoniazid concentrations
- Isoniazid and beta adrenergic blockers = Increased isoniazid effects
- Isoniazid and corticosteroids = Decreased isoniazid levels
- Isoniazid and meperidine = Hypotension or CNS depression
- Isoniazid and valproic acid = Increased toxic effects of both agents
- Isoniazid and ketoconazole = Ketoconazole' s therapeutic benefit may be attenuated
- Isoniazid and theophylline = Altered theophylline concentrations
- Isoniazid and theophylline = Increased risk of respiratory paralysis and renal dysfunction
- Isoniazid and aminosalicyclic acid = Increased isoniazid serum concentrations
- Capreomycin and phenothiazines = Increased risk of respiratory paralysis
- Rifamycins and acetaminophen = Decreased effectiveness and enhanced hepatic toxicity of acetaminophen
- Rifamycins and losartan, clozapine, dapsone, oral contraceptives, non-nucleoside reverse transcriptase inhibitor, sertraline, thyroid hormones, zidovudine, zolpidem, and amiodarone = Rifamycins increasing other drugs' metabolism reducing it's effects
- Ethambutol and aluminum salts = Aluminum salts delay and reduce the absorption
- Pyrazinamide and cyclosporine = Whole blood cyclosporine concentrations decreased
- Dapsone and didanosine = Possible therapeutic failure of dapsone
- Dapsone and Para-aminobenzoic acid – Dapsone suppression of Plasmodium infections

VI. Adverse Drug Events[5]

Table 6. Common Adverse Events Reported for the Single Entity Antimycobacterials

Adverse Event	Ethambutol	Pyrazinamide	Rifampin	Capreomycin	Isoniazid	Rifabutin	Dapsone
Body as a Whole							
Malaise	X		X				
Cardiovascular							
Edema							
Hypotension							
Hypertension							
Digestive System							
Abdominal Pain	X		X			4	X
Nausea / Vomiting	X	X	X		X	6	X
Diarrhea			X			3	
Epigastric distress	X		X		X		
Appetite decrease		X				2	X
Central Nervous System							
Dizziness/Vertigo	X						X
Fatigue			X				
Fever	X	X	X			2	X
Headache	X		X			3	X
Meningeal Signs							
Raised Intracranial Pressure							
Collapse							
Confusion	X		X				
Drowsiness						1	
Hepatic							
Abnormal LFTs (incr.)	X	X	X	X	X		
Hepatitis			X		X		
Jaundice					X		
Hepatic failure					X		
Skin and Appendages							
Alopecia							
Rash			X			11	
Pruritus			X				
Hematologic							
Neutropenia							
Agranulocytosis					X		
Renal							
Abnormal kidney fxn			X	X			
Acute kidney failure							
Other							
Angioedema							
Convulsions							

Selected others:

X = Incidence reported, specific percentages not available.

Rifabutin = discolored urine

Dapsone= peripheral neuropathy, drug induced lupus erythematosus, phototoxicity, dose-related hemolysis, hypoalbuminemia, albuminuria, nephrotic syndrome, renal papillary necrosis, blurred vision, tinnitus, male infertility, tachycardia, pancreatitis, mononucleosis-like syndrome

Isoniazid = Hepatitis Box Warning, pyridoxine deficiency, peripheral neuropathy, agranulocytosis, anemia (hemolytic, sideroblastic, or aplastic), thrombocytopenic, eosinophilia, systemic lupus erythematosus-like syndrome, skin eruptions, rheumatic syndrome

Capreomycin = Eighth Cranial Nerve Damage Box Warning, leukocytosis, leukopenia, tinnitus, vert igo

Rifampin = 'flu-like; syndrome, hematopoietic reactions, flushing, pseudomembranous colitis, thrombocytopenia, muscular weakness, myopathy, ataxia, psychosis, interstitial nephritis, acute tubular necrosis, visual disturbances, menstrual disturbances

Pyrazinamide = hyperuricemia, thrombocytopenia, sideroblastic anemia, myalgia, mild arthralgia, dysuria, porphyria, photosensitivity

Ethambutol = peripheral neuritis, elevated serum uric levels, gout, Optic neuritis (decrease visual acuity), joint pain

Table 6 (con't). Common Adverse Events Reported for the Single Entity Antimycobacterials

Adverse Event	Clofazimine	Aminosalicyclic	Ethionamide	Cycloserine	Rifapentine
Body as a Whole					
Malaise					
Cardiovascular					
Edema					
Hypotension					
Hypertension					
Digestive System					
Abdominal Pain	X	X	X		X
Nausea / Vomiting	X	X	X		X
Diarrhea	X	X	X		
Epigastric distress	X		X		
Appetite decrease			X		X
Central Nervous System					
Dizziness/Vertigo	X		X	X	
Fatigue	X			X	
Fever		X			
Headache	X		X		
Meningeal Signs					
Raised Intracranial Pressure					
Collapse					
Confusion				X	
Drowsiness	X		X	X	
Hepatic					
Abnormal LFTs (incr.)			X	X	X
Hepatitis	X	X	X		
Jaundice	X	X	X		
Hepatic failure					
Skin and Appendages					
Alopecia					
Rash	X	X			X
Pruritus	X				X
Hematologic					
Neutropenia					
Agranulocytosis					
Renal					
Abnormal kidney fxn					
Acute kidney failure					
Other					
Angioedema					
Convulsions				X	

Selected others:
X = Incidence reported, specific percentages not available.
Rifapentine= hyperbilirubinemia, pseudomembranous colitis, pancreatitis, neutropenia, leukopenia, thrombocytopenia, discolored body fluids, hyperbilirubinemia, and proteinuria, Note: Most side effects reported with combination therapy
Cycloserine = CNS effects, CHF
Ethionamide = Psychotic disturbances, peripheral neuritis, postural hypotension, thrombocytopenia, hypoglycemia, pellagra-like syndrome, metallic taste, stomatitis, excessive salivation, weight loss, blurred vision, diplopia, otic neuritis
Aminosalicyclic = infectious mononucleosis-like or lymphoma-like syndrome, leukopenia, agranulocytosis, thrombocytopenia, Coombs' positive hemolytic anemia, pericarditis, hypoglycemia, optic neuritis, encephalopathy, Loeffler syndrome, vasculitis, prothrombin reduction
Clofazimine = taste disorders, skin pigmentation, ichthyosis, phototoxicity, bowel obstruction, GI bleeding, constipation weight loss, enlarged liver, conjunctival and corneal pigmentation, depression, splenic infarction, thromboembolism anemia, discolored body fluids, lymphadenopathy, vascular pain

VII. Dosing and Administration of the Single Entity Antimycobacterials

Table 7. Dosing for the Single Entity Antimycobacterials[5]

Drug	Availability	Dose (maximum dose)*
Isoniazid	Tablets (50, 100, 300mg); elixir (50mg/5ml); aqueous solution for IV or IM	Daily dose: 5mg/kg (300mg); 11 doses /wk, 2 doses /wk or 3 doses / wk: 15mg/kg (900mg)
Rifampin	Capsules (150 and 300mg); aqueous solution for IV	Daily dose, 2 doses / wk, or 3 doses /wk: 10mg/kg (600mg)
Rifabutin	Capsule (150mg)	Daily dose, 2 doses / wk, or 3 doses / wk: 5mg/kg (300mg)
Rifapentine	Tablet (150mg, film coated)	11 doses/ wk during continuation phase: 10mg/kg (600mg)
Pyrazinamide	Tablet (500mg, scored)	45-55 kg = daily dose: 1000mg; 2 doses / wk: 2000mg; 3 doses / wk: 1500mg 56-75 kg = daily dose: 1500mg; 2 doses / wk: 3000mg; 3 doses / wk: 2500mg 76-90 kg = daily dose: 2000mg; 2 doses / wk: 4000mg; 3 doses / wk: 3000mg
Ethambutol	Tablet (100 and 400mg)	45-55 kg = daily dose: 800mg; 2 doses / wk: 2000mg; 3 doses / wk: 1200mg 56-75 kg = daily dose: 1200mg; 2 doses / wk: 2800mg; 3 doses / wk: 2000mg 76-90 kg = daily dose: 1600mg; 2 doses / wk: 4000mg; 3 doses / wk: 2400mg
Cycloserine	Capsule (250mg)	Daily Dose: 10-15mg/kg/d (1g in 2 doses), usually 500-750mg/d in 2 doses
Ethionamide	Tablet (250mg)	Daily Dose: 15-20mg/kg/d (1g/d) in 1-2 divided doses
Capreomycin	Aqueous solution for IV or IM	15-30mg/ kg/d (1g/d)
Aminosalicylic acid	Granules (4g packets)	8-12g/d in 2 or 3 doses
Dapsone	Tablets (25 & 100mg)	Leprosy TX: 100mg/d for 2 years; Leprosy Prevention: 50mg/d; dermatitis herpetiformis: 50mg/d (300mg/d
Clofazimine	Capsules (50mg)	Leprosy 100-200mg/d in combination with other drugs

*Dose per weight is based on ideal body weight. Children weighing more than 40kg should be dosed as adults.

Special Dosing Considerations

Table 8. Special Dosing Considerations for the Single Entity Antimycobacterials[5,6]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use*	Pregnancy Category	Can Drug Be Crushed?
Isoniazid	Y	Y	Children (max.): Daily dose: 10-15 mg/kg (300 mg); 2 doses / wk: 20-30 mg (900 mg)	C	-
Capreomycin sulfate	Y	-	Children (max.): Daily or 2 doses /wk: 15-30 mg/ kg/d (1g/d)	C	N/A
Rifabutin	Y	-	Appropriate dosing for children is unknown.	B	N/A
Aminosalicyclic acid	Y	-	200-300 mg/kg/d in 2-4 divided doses (10g)	C	No, granules are enteric-coated
Rifapentine	Y	-	No	C	-
Pyrazinamide	Y	Y	Children (max): Daily dose: 15-30 mg/ kg (2g.); 2 doses / wk: 50 mg / kg (2gm)	C	-
Rifampin	Y	Y	Children (max): Daily or 2 doses / wk: 10-20 mg/kg (600 mg)	C	No information about crushing noted, however a suspension could be prepared.
Cycloserine	Y	-	Children (max): 10-15 mg/kg/d (1g/ d)	C	N/A
Ethionamide	Y	-	15-20 mg/kg/d (1g/d)	C	-
Dapsone	N	-	Leprosy TX: 1-2mg/kg/d (100mg/d)	C	-
Clofazimine	-	Y	No	C	N/A
Ethambutol	Y	-	Children (max): Daily or 2 doses /wk: 10-20 mg/kg/d (1g/d)	C	-

VIII. Comparative Effectiveness

Isoniazid, ethambutol, rifampin, and pyrazinamide are the drugs used most frequently in the treatment of tuberculosis. Rifapentine and rifabutin are used as alternatives to rifampin in multiple-drug antituberculosis regimens. Aminosalicylic acid, capreomycin, cycloserine, and ethionamide are more toxic and less effective than the primary antituberculosis agents and are used when the primary agents are contraindicated or are ineffective because of resistance.[8] Table 9 illustrates comparative studies for the single entity antimycobacterials.

Table 9. Outcomes Evidence for the Single Entity Antimycobacterials

Study	Sample	Treatment / Duration	Results
Johnson JL, et al.[9]	n=2736	Isoniazid for 6 months (6H), isoniazid and rifampicin for 3 months (3HR), isoniazid and rifampicin and pyrazinamide for 3 months (3HRZ), or placebo for 6 months	In assessing the efficacy of three treatment regimens in treating latent tuberculosis in HIV-infected patients: • 6H initially protected against tuberculosis; however, benefit was lost within the first year of treatment. • Sustained benefit was observed in persons receiving 3HR and 3HRZ with no significant difference among the two groups. • Treatment of latent tuberculosis infection had no effect on mortality.
Research Committee of the British Thoracic Society[10]	n=223	Rifampicin and ethambutol (RE) or rifampicin, ethambutol, and isoniazid (REH) for 2 years with up to 5	In testing the effectiveness of two regimens in HIV-negative patients for treating pulmonary disease caused by *M. avium intracellular* (MAC), *M. malmoense*, and *M. xenopi*, in this randomized study: • No significant difference between groups in the number of deaths for each species, but when the three species were combined there were fewer deaths from the mycobacterial disease with the RE group.

		years follow-up	• Failure of treatment/relapse rates did not differ between groups for *M. malmoense*, but for MAC there were significantly fewer failures of treatment/relapses with REH. Failure of treatment/relapse rates showed a non-significant trend in favor of REH and when all three species were combined there was a significant difference in favor of REH.
Gordin F, et al.[11]	n=1583	Rifampin 600mg daily and pyrazinamide 20mg/kg/day for 2 months or isoniazid 300mg daily with pyridoxine for 12 months	In evaluating the efficacy of two different therapy courses for prevention of tuberculosis in persons with HIV-1 infection, in this randomized, open-label controlled trial: • Statistically significantly more patients in the rifampin and pyrazinamide group completed therapy compared with the isoniazid group. • No significant differences between groups in rates of confirmed or probable tuberculosis, HIV progression, and/or death, or overall adverse events, although drug discontinuation was slightly higher in the rifampin and pyrazinamide group. • Neither group appeared to lead to the development of drug-resistant tuberculosis.
Halsey NA, et al.[12]	n=750	Isoniazid for 6 months or rifampicin and pyrazinamide for 2 months with up to 4 years follow-up	In testing the efficacy of isoniazid versus rifampicin with pyrazinamide for prevention of tuberculosis in HIV-1-positive individuals: • No statistically significant difference between groups for incidence of tuberculosis. • Risk of tuberculosis during the first 10 months after study entry was statistically significantly higher in the rifampicin and pyrazinamide group compared with the isoniazid group. • No statistically significant difference in risk of tuberculosis at 36 months after study entry between the groups. • No significant differences in total mortality at any time.
Hawken MP, et al.[13]	n=684	Isoniazid 300mg daily or placebo for 6 months	In determining the efficacy of isoniazid in the prevention of tuberculosis in HIV-1 infected adults and whether tuberculosis preventive therapy prolongs survival, in this randomized, double-blind placebo controlled trial: • No statistically significant difference between groups for incidence of tuberculosis. • No statistically significant difference between groups for mortality rate. • The rate of drug resistance observed in subjects who received isoniazid and subsequently developed tuberculosis was low.
Santha T, et al.[14]	n=1240	Rifampicin + ethambutol given on one day and isoniazid + pyrazinamide the next day for the first 2 months followed by rifampicin + isoniazid twice weekly for 4 months (split I), or same drugs in split I, except duration was 3 months in each phase (split II), or rifampicin, isoniazid, ethambutol, and pyrazinamide, given thrice weekly for 2 months followed by isoniazid and rifampicin twice weekly for 4 months (split III) with up to 5 years follow-up	In evaluating the efficacy of split-drug regimens for treatment of patients with sputum smear-positive pulmonary tuberculosis, in this randomized controlled clinical trial: • Negative cultures were observed in 91% of split I patients, 94% of split II patients, and 89% of split III patients. • Significantly more gastrointestinal symptoms were found among patients taking the split III regimen.
Balasubramanian R, et al.[15]	n=193	Rifampicin, isoniazid, and pyrazinamide for 2 months followed by	In assessing and comparing the efficacy of a 6-month short-course chemotherapy regimen with that of a 12-month standard regimen in the treatment of abdominal tuberculosis: • Clinical status was normal in 99% in 6R patients and in 94% in 12E

		rifampicin with isoniazid for another 4 months (6R), or 12 month standard regimen of ethambutol and isoniazid with streptomycin supplemented for 2 weeks (12E)	patients. • No patients had relapsed in either group at the end of the follow-up period.
Yuen AP, et al.[16]	n=113	Thrice weekly 6-months of streptomycin, isoniazid, rifampicin, and pyrazinamide for 4 months followed by isoniazid and rifampicin for 2 months or thrice weekly 9-months of streptomycin, isoniazid, rifampicin, and pyrazinamide for 4 months followed by isoniazid and rifampicin for 5 months	In comparing the efficacy of a 6-month or a 9-month regimen for the treatment of cervical tuberculous lymphadenopathy: • Primary treatment failure occurred in 5% in the 6-month regimen and 2% in the 9-month regimen. • At 5 years follow-up, patients still in remission included 89% in the 6-month regimen and 90% in the 9-month regimen. • There were no significant differences of both primary failure rate and 5-year actuarial remission rate of the 2 regimens.
Shafran SD, et al.[17]	n=229	Rifampin, ethambutol, clofazimine, and ciprofloxacin or rifabutin, ethambutol, and clarithromycin for 4 weeks	In comparing the efficacy of two regimens for the treatment of *Mycobacterium avium* complex (MAC) bacteremia in AIDS patients: • Significantly more negative blood cultures were found with the 3-drug regimen. • Bacteremia resolved significantly more frequently in the 3-drug group. • Survival was significantly longer in the 3-drug group compared with the 4-drug group.
Benator D, et al.[18]	n=1004	Once weekly rifapentine and isoniazid or twice weekly rifampicin and isoniazid for 2 months with 2 year follow-up	In comparing the efficacy of two regimens for the treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: • Significantly fewer patients experienced failure/relapse in the twice weekly group compared with the once weekly group. • In patients without cavitation, rates of failure/relapse were similar among groups. • Rates of adverse events and death were similar in the two treatment groups.
Benson CA, et al.[19]	n=1178	Clarithromycin, or rifabutin, or clarithromycin plus rifabutin	In evaluating the efficacy and safety of therapy for prevention of *Mycobacterium avium* complex (MAC) disease in AIDS patients, in this randomized, double-blind, placebo-controlled trial: • MAC disease occurred in 9%, 15%, and 7% of those randomized to clarithromycin or rifabutin alone or in combination, respectively. • Risk of MAC disease was significantly reduced more by clarithromycin and combination therapy compared with rifabutin; however, combination therapy was not more effective than clarithromycin alone. • There were no survival differences among groups.
Gordin FM, et al.[20]	n=198	Clarithormycin 500mg twice daily plus ethambutol 1200mg daily with or without rifabutin 300 mg daily	In assessing the efficacy of therapy for treating disseminated Mycobacterium avium complex (MAC): • Changes in clinical symptoms and time to survival were similar in both groups. • No significant differences in bacteriologic response among groups. • Development of clarithromycin resistance during therapy was similar in the two groups; of patients who had a bacteriologic response, significantly fewer patients in the rifabutin group developed clarithromycin resistance.

McGregor MM, et al.[21]	n=298	Isoniazid, ethambutol, and pyrazinamide with either rifampicin or rifabutin for 24 weeks.	In comparing the efficacy and safety of rifabutin and rifampicin in patients with newly diagnosed pulmonary tuberculosis: • No significant differences were found in bacteriologic conversion rates among groups. • Overall rate of relapse at 24 months was not significantly different among groups.
Havlir DV, et al.[22]	n=693	Rifabutin, azithromycin, or both	In evaluating the efficacy of prophylaxis against disseminated *Mycobacterium avium* complex (MAC) in HIV-infected patients, in this multicenter, double-blind, randomized trial: • The incidence of disseminated MAC infection at 1 year was 15.3% with rifabutin, 7.6% with azithromycin, and 2.8% with both drugs. • Survival was similar in all three groups.
Benson CA, et al.[23]	n=160	Clarithromycin with either ethambutol (C+E), rifabutin (C+R), or both (C+E+R) for 48 weeks	In evaluating the safety and efficacy of three clarithromycin-containing combination regimens for the treatment of disseminated *Mycobacterium avium* complex (MAC) disease in persons with acquired immunodeficiency syndrome, in this mutlicenter, randomized, open-label trial: • Proportion of subjects with a complete microbiologic response was not statistically significantly different among treatment arms. • Proportion of patients with complete or partial responses who experienced a relapse while receiving C+R was significantly higher than that of patients receiving C+E+R and marginally higher than that of patients receiving C+E. • Subjects in the C+E+R group had improved survival, compared with the patients receiving C+E and the C+R groups.
Goodgame RW, et al.[24]	n=31	Clarithromycin 500mg twice daily and ethambutol 15mg/kg daily, or placebo for 3 months	In assessing the effectiveness of test therapy on the disease activity and intestinal permeability in patients with Crohn's disease at high risk of relapse: • No differences between the drug or placebo groups in the mean Harvey-Bradshaw index, number with active disease, and mean lactulose-mannitol test. • During the 12-month follow-up period, there were no consistent, statistically significant differences in the mean Harvey-Bradshaw index or lactulose-mannitol test between the treatment and placebo groups.
Dube MP, et al.[25]	n=95	Clarithromycin plus clofazimine, with or without ethambutol	In evaluating ethambutol therapy in preventing relapse and drug resistence during treatment of *Mycobacterium avium* complex bacteremia with clarithromycin-based combination therapy: • Nine relapses occurred in the two-drug arm compared with three relapses in the three-drug arm. Estimated risk of relapse was statistically significantly higher in the two-drug arm. • All relapse isolates were resistant to clarithromycin. • Median time to clarithromycin resistance was 16 weeks with two drugs and 40 weeks with three drugs.
Katoch K, et al.[26]	n=300	Rifampicin monthly with daily dapsone or rifampicin monthly with dapsone and clofazimine daily for 6 months	In assessing the effectiveness of clofazimine therapy in patients with paucibacillary leprosy: • After 6 months of therapy, lesion activity persisted in 7.5% of patients in the clofazamine containing regimen compared with 16% in the control regimen. • Lesion activity subsided more rapidly in the clofazamine group compared with the control group. • During follow-up of 2.5 to 3.5 years, there were no relapses in the clofazimine containing group compared with two relapses in the control group.

Additional Evidence

Dose Simplification: The prinicipal reason why cures are not achieved with available drug regimens for tuberculosis is patient noncompliance or failure to complete the prescribed regimen. Since shortening the total duration of chemotherapy is a potential means of combating this problem, the American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) currently recommend short-course (minimum of 6 months) chemotherapy regimens as preferred alternatives to more prolonged conventional regimens (18-24 months) for the initial treatment of uncomplicated pulmonary and most cases of extrapulmonary tuberculosis in adults. One study compared treatment of pulmonary tuberculosis with either rifapentine and isoniazid once a week or rifampicin and isoniazid twice a week. In this study, twice weekly therapy was more effective in regards to failure/relapse rates with once weekly therapy.[18]

Stable Therapy: A literature search of Medline did not reveal clinical literature relevant to changing therapies once stabilized on an antimycobacterial regimen for tuberculosis. However, one study comparing atovaquone with dapsone for the prevention of *Pneumocystic carinii* pneumonia in patients with HIV infection found that in patients who were receiving dapsone therapy at baseline, significantly more patients in the atovaquone group discontinued therapy due to adverse effects compared with those patients continuing dapsone therapy.[27]

Impact on Physician Visits: The CDC recommends that directly observed therapy (DOT) be used whenever possible to ensure compliance. Therefore, any methods to decrease number of visits, such as short-course chemotherapy regimens will impact physician visits. However, a literature search of Medline did not reveal clinical literature relevant to use of the antimycobacterials and their impact on physician visits.

IX. Conclusions

First-line agents for the treatment of tuberculosis include combinations of isoniazid, rifampin, rifapentine, pyrazinamide, and ethambutol. Second-line agents are cycloserine and ethionamide. All of the first-line agents (except for rifapentine) are available in generic formulations. The second-line agents (for use in resistant tuberculosis) should be made available through medical justification through the prior authorization program. Additionally, treatment of Leprosy and Mycobacterium avium complex (MAC) with the drugs in this class is not within the scope of general use; however, these drugs should be available for their indicated special needs/circumstances via medical justification through the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand single entity antimycobacterial is recommended for preferred status.

Pharmacotherapy Review of the Antimycobacterials
Combination Agents
AHFS 081600, 081604, 081692

I. Overview

Mycobacteria are unusual bacteria with a waxy cell wall structure, making them difficult to stain and for antimycobacterials to penetrate their cell walls. Mycobacteria are very slow growing, also hindering antimycobacterial activity. Drug resistance occurs primarily due to point mutations in the bacterial chromosome. Multiple combination antimycobacterials are often used to combat drug resistance. Antimycobacterials often have unpleasant adverse drug effects that can lead to poor compliance and contributes to emergence of resistant strains. Combination products aid compliance, reducing treatment failures.

Tuberculosis (TB) is a common disease transmitted by inhaling airborne bacilli, *Mycobacterium tuberculosis*, from an active infective TB patient and has emerged as the single leading cause of death from any single infectious agent.[1] It is estimated that one-third of the world's population is latently infected.[1,2] The United States has undergone TB resurgence due to many factors, including the immunodeficiency virus (HIV) pandemic and increases in the number of cases reported with foreign born people. Reduction in cell-mediated immunity associated with HIV infection is considered to be the greatest risk factor for the activation of latent TB. Increased prevalence of multidrug resistant tuberculosis (MDR-TB) is a serious concern in the United States leading to outbreaks, especially in HIV infected people.

After being transmitted, *M. tuberculosis* multiplies in the alveolus and is carried by macrophages, lymphatics, and blood to various sites (e.g. Lung pleura, brain, kidney, and bone). Latent tuberculosis infection (LTBI) is asymptomatic and noninfectious but is usually detected by a positive skin test. Active TB occurs in 10% of infected individuals without preventive therapy.[3] The likelihood of active infection increases with immunosuppression and is highest for all individuals within two years after infection. Eighty-five percent of cases are pulmonary, which is infectious.[3] Primary TB is disease resulting from the initial pulmonary infection that the immune system is unable to control. Recrudescent TB is active disease occurring after a latent asymptomatic period.

This review encompasses all combination antimycobacterial dosage forms and strengths.

Table 1. Combination Antimycobacterials in this Review

Generic Name	Formulation	Example Brand Name
Isoniazid/rifampin	Capsules (150mg/300mg)	Rifamate
Isoniazid/pyrazinamide/rifampin	Tablets (50mg/300mg/120mg)	Rifater

No generic formulations are available for either drug in this class.

II. Evidence Based Medicine and Current Treatment Guidelines[6]

American Thoracic Society, Centers for Disease Control and Prevention (CDC), and Disease Society of America's guidelines are considered to be the standard of practice for TB treatment. Overall treatment goals are to cure the individual patient and to minimize the transmission of *Mycobacterium tuberculosis* to others. The successful treatment of TB has benefits for the individual patient and the community. Prescribing physician responsibility for treatment completion is a fundamental treatment principle. Patient-centered care should always include an adherence plan that emphasized directly observed therapy (DOT), in which patients are observed to ingest each dose of anti-TB medications to maximize the likelihood of therapy completion.

Anti-TB drugs have three areas of activity: bactericidal, sterilizing, and drug resistance prevention. Isoniazid is the most potent bactericidal agent, and rifampin has some bactericidal activity. Rifampin and pyrazinamide are the most potent sterilizing drugs. The recommended treatment

regimens for drug susceptible organisms are divided into two phases. Rapidly multiplying *M. tuberculosis* is killed during the initial phase of two months. Sterilizing drugs kill the intermittently dividing *M. tuberculosis* during the continuation phase of four or seven months. Multiple drugs are used due to possible drug resistance.

First line medications include isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, and ethambutol. Second line medications include cycloserine and ethionamide.

First line anti-TB medications should be administered together and dose splitting should be avoided. Combination medications may be administered more easily than single medications, and aid in patient compliance thereby possibly reducing acquired resistance. First line anti-TB medications should not be discontinued for minor side effects such as gastrointestinal upset. Medications may be taken with food to decrease gastrointestinal upset, although food may delay or moderately decrease medication absorption. Drug induced hepatitis is the most severe common adverse effect.

Table 2. Drug Regimens for Culture Positive Pulmonary Tuberculosis Caused by Drug Susceptible Organisms [6]

Initial Phase			**Continuation Phase**			**Range of Total doses (minimal duration)**	**Rating* (evidence)#**	
Regimen	Drugs	Interval & doses^ (minimal duration)	Regimen	Drugs	Interval & doses ^ς (minimal duration)		HIV-	HIV+
1	IHN RIF PZA EMB	7 d /wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	1a	INH/ RIF	7 d/wk for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶	182-130 (26 wk)	A (I)	A (II)
			1b	INH/ RIF	2 d/wk for 36 doses (18 week)	92-76 (26 wk)	A (I)	A (II)•
			1c‡	INH/ RPT	1 d /wk for 18 doses	74-58 (26 wk)	B (I)	E (I)
2	IHN RIF PZA EMB	7 d/wk for 14 doses (2 wk), then 2 d/wk for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)¶, then 2 d/wk for 12 doses (6 wk)	2a	INH/ RIF	2 d/wk for 36 doses (18 wk)	62-58 (26 wk)	A (II)	B (II)•
			2b‡	INH/ RPT	1 d/wk fro 18 doses (18 wk)	44-40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	3 d/wk for 24 doses (8 wk)	3a	INH/ RIF	3 d/wk for 54 doses (26 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶	4a	INH/ RIF	7 d/wk for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶	273-195 (39 wk)	C (I)	C (II)
			4b	IHN/ RIF	2 d/wk for 62 doses (31 wk)	118-102 (39 wk)	C (I)	C (II)

Drug Abbreviations: EMB=Ethambutol; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; RPT=rifapentine

* Definitions of evidence ratings: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; E= should never be given

Definition of evidence ratings: I=randomized clinical trial; II=data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion

^When DOT is used, drugs may be given 5 d/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with 7 daily doses, extensive experience indicates this would be an effective practice.

ς Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 wk), either 217 doses (daily) or 62 doses (2 d/wk) continuation phase.

¶ Five-day-a-week administration is always given by DOT. Rating for 5 d/wk regimens is A (III)

• Not recommended for HIV-infected patients with CD4+ cells counts <100 cells/ul.

‡Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

III. Indications of the Combination Antimycobacterial Agents

Table 3. FDA-Approved Indications for the Single Entity Antimycobacterials[5]

Drug	Tuberculosis
Rifampin, isoniazid, pyrazinamide	X
Rifampin / isoniazid	X

IV. Pharmacokinetics of the Combination Antimycobacterial Agents

Table 4 describes the pharmacokinetic parameters of each component of the combination agents.

Table 4. Pharmacokinetic Parameters of the Combination Antimycobacterials[5]

Drug	Mechanism of Action	Bioavailability	Protein Binding	Metabolism	Active Metabolites
Isoniazid	Inhibits mycolic acids synthesis	Rapid and complete absorption	10-15%	Hepatic Acetylation and dehydrazination	N-acetylisoniazid
Pyrazinamide	Exact mechanism not known, but lowers pH by conversion to pyrazine acid	Well absorbed	50%	Hepatic hydroxylation	Pyrazinoic acid
Rifampin	Suppress RNA synthesis by inhibiting DNA-dependent RNA polymerase	N/A	80%	Hepatic deacetylation	Desacetyl-rifampicin

V. Drug Interactions of the Combination Antimycobacterial Agents

Table 5. Significant Drug Interactions of the Combination Antimycobacterials[7]

Drug	Significance	Interaction	Mechanism
Isoniazid	Level 2 (delayed, moderate, suspected)	Isoniazid and chlorzoxazone	Isoniazid may inhibit hepatic metabolism (CYP2E1) elevating plasma concentrations, increasing the therapeutic and adverse effects.
Isoniazid	Level 2 (rapid, moderate, suspected)	Isoniazid and enflurane	Rapid acetylation of isoniazid produces high concentration of hydrazine that facilitates deflurination of enflurane. High output renal failure may occur due to nephrotoxic concentrations in rapid isoniazid acetylators.
Isoniazid	Level 2 (delayed, moderate, established)	Isoniazid and hydantoins	Isoniazid inhibits the hepatic microsomal enzyme metabolism of hydantoins. Serum hydantoins levels may be increased resulting in increased pharmacologic and toxic effects of hydantoins.
Isoniazid	Level 1 (delayed, major, probable)	Isoniazid and rifampin	Possible alternation in Isoniazid metabolism. Hepatotoxicity may occur at a higher rate than with either agent alone.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and amprenavir	Amprenavir may decrease rifamycins metabolism while rifamycins increase amprenavir metabolism.
Rifamycins‡	Level 2 (delayed, moderate, established)	Rifamycins and anticoagulants	Increased hepatic metabolism of anticoagulants resulting in decreased anticoagulation actions.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and azole antifungals	Rifamycins may induce metabolism of azole antifungals while ketoconazole may interfere with rifamycin absorption and itraconazole may inhibit rifamycin metabolism. Plasma levels of azole antifungals may be decrease; ketoconazole may decrease rifamycin levels; itraconazole may increase rifamycins levels.
Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and beta-blockers, quinine derivatives, sulfonylureas, and propafenone	Possibly due to increased hepatic metabolism induced by rifamycins resulting in reduced pharmacologic effects.

Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and buspirone	Induction of first pass metabolism of buspirone by rifamycins resulting in decreased buspirone plasma concentrations and pharmacologic effects.
Rifamycins‡	Level 1 (delayed, major, established)	Rifamycins and corticosteroids, and theophylline	Rifamycins may increase hepatic metabolism resulting in decreased effects.
Rifamycins‡	Level 1 (delayed, major, probable)	Rifamycins and cyclosporine	Rifamycins increase hepatic and intestinal metabolism of cyclosporine resulting in reduced immunosuppressive effects for cyclosporine.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and estrogens	Rifamycins induce hepatic drug metabolizing enzymes of estrogens increasing 4-fold in vitro and in vivo. AUC and half-life also are decreased. Rifamycins may impair the effectiveness of estrogens; menstrual disturbances have been noted.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and haloperidol, HMG-CoA Reductase Inhibitors, hydantoins, delavirdine, indinavir, lamotrigine, doxycycline, benzodiazepines, meglitnides, nelfinavir, ondansetron, ritonavir, saquinavir, tricyclic antidepressants, tamoxifen, and toremifene	Metabolism induction decreasing plasma concentrations and effectiveness.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and macrolide antibiotics	Rifamycins' metabolism may be inhibited while macrolide metabolism may be increased. The antimicrobial effects of the macrolide may be deceased while the frequency of adverse GI reactions and adverse effects of rifamycins may be increased.
Rifamycins‡	Level 2 (delayed, moderate, suspected)	Rifamycins and morphine	Unknown mechanism. Decreased morphine analgesic effects.
Rifamycins‡	Level 2 (delayed, moderate, probable)	Rifamycins and nifedipine	Possibly caused by increased gut wall metabolism (cytochrome P450 3A4) induced by rifamycins resulting in reduced therapeutic effects.
Rifamycins‡	Level 1 (delayed, major, probable)	Rifamycins and tacrolimus	Possible hepatic and intestinal metabolism (CYP3A4) induced by rifamycins. The immunosuppressive effects of tacrolimus may be reduced as early as 2 days after starting rifamycins.
Rifamycins‡	Level 1 (delayed, major, suspected)	Rifamycins and voriconazole	Rifamycins increase the metabolism of voriconazole, and voriconazole inhibits the metabolism of rifamycins. Voriconazole plasma concentrations may be reduced, decreasing the therapeutic effect and Rifamycins' plasma levels may be elevated increasing the risk of side effects.

‡ Rifamycins include rifabutin, rifapentine, and rifampin.

Other Interactions:

- Isoniazid and acetaminophen = Increased hepatotoxicity
- Isoniazid and anticoagulants = Enhanced anticoagulant activity
- Isoniazid and benzodiazepines = Enhanced benzodiazepine effect
- Isoniazid or ethionamide, and cycloserine = Increased cycloserine CNS side effects
- Isoniazid and disulfiram = Acute behavioral and coordination changes
- Isoniazid and aluminum salts = Decreased isoniazid concentrations
- Isoniazid and beta adrenergic blockers = Increased isoniazid effects
- Isoniazid and corticosteroids = Decreased isoniazid levels
- Isoniazid and meperidine = Hypotension or CNS depression
- Isoniazid and valproic acid = Increased toxic effects of both agents
- Isoniazid and ketoconazole = Ketoconazole' s therapeutic benefit may be attenuated
- Isoniazid and theophylline = Altered theophylline concentrations
- Isoniazid and theophylline = Increased risk of respiratory paralysis and renal dysfunction
- Isoniazid and aminosalicyclic acid = Increased isoniazid serum concentrations

- Rifamycins and acetaminophen = Decreased effectiveness and enhanced hepatic toxicity of acetaminophen
- Rifamycins and losartan, clozapine, dapsone, oral contraceptives, non-nucleoside reverse transcriptase inhibitor, sertraline, thyroid hormones, zidovudine, zolpidem, and amiodarone = Rifamycins increasing other drugs' metabolism reducing it's effects
- Pyrazinamide and cyclosporine = Whole blood cyclosporine concentrations decreased

VI. Adverse Events of the Combination Antimycobacterial Agents

Table 6. Common Adverse Events Reported for the Combination Antimycobacterials

Adverse Event	Pyrazinamide	Rifampin	Isoniazid
Body as a Whole			
Malaise		X	
Cardiovascular			
Edema			
Hypotension			
Hypertension			
Digestive System			
Abdominal Pain		X	
Nausea / Vomiting	X	X	X
Diarrhea		X	
Epigastric distress		X	X
Appetite decrease	X		
Central Nervous System			
Dizziness/Vertigo			
Fatigue		X	
Fever	X	X	
Headache		X	
Meningeal Signs			
Raised Intracranial Pressure			
Collapse			
Confusion		X	
Drowsiness			
Hepatic			
Abnormal LFTs (incr.)	X	X	X
Hepatitis		X	X
Jaundice			X
Hepatic failure			X
Skin and Appendages			
Alopecia			
Rash		X	
Pruritus		X	
Hematologic			
Neutropenia			
Agranulocytosis			X
Renal			
Abnormal kidney fxn		X	
Acute kidney failure			
Other			
Angioedema			
Convulsions			

Selected others:
X = Incidence reported, specific percentages not available.
Isoniazid = Hepatitis Box Warning, pyridoxine deficiency, peripheral neuropathy, agranulocytosis, anemia (hemolytic, sideroblastic, or aplastic), thrombocytopenic, eosinophilia, systemic lupus erythematosus-like syndrome, skin eruptions, rheumatic syndrome
Rifampin = 'flu-like; syndrome, hematopoietic reactions, flushing, pseudomembranous colitis, thrombocytopenia, muscular weakness, myopathy, ataxia, psychosis, interstitial nephritis, acute tubular necrosis, visual disturbances, menstrual disturbances
Pyrazinamide = hyperuricemia, thrombocytopenia, sideroblastic anemia, myalgia, mild arthralgia, dysuria, porphyria, photosensitivity.

VII. Dosage and Administration of the Combination Antimycobacterial Agents

Table 7. Dosing for the Combination Antimycobacterials[5]

Drug	Availability	Daily Dose
Rifater	Tablets (120mg rifampin, 50mg isoniazid, 300mg pyrazinamide)	<45kg: 4 tablets; 45-54 kg: 5 tablets; >54kg: 6 tablets
Rifamate	Capsules (300mg rifampin and 150mg isoniazid	2 capsules

VIII. Comparative Efficacy of the Combination Antimycobacterial Agents

Treatment of tuberculosis involves therapy with multiple medications. Treatment requires at least two drugs to retard the development of drug resistance.[28] In the United States, only 15-18% of rifampin is sold in a fixed-dose combination product. Additionally, there have been problems with these drugs because their names are so similar to rifampin. Mistakes in prescribing and dispensing can result in patients receiving incorrect treatment.

Many of the studies presented in the single-entity antimycobacterial review looked at treatment with combination therapy. See Table 9 above in the single entity review for efficacy studies of combination drugs in this class. Rifater and Rifamate are both indicated for the treatment of tuberculosis. Table 8 describes the limited clinical efficacy of these drugs.

Table 8. Outcomes Evidence for the Combination Antimycobacterials

Study	Sample	Treatment / Duration	Results
Su WJ, et al.[29] Randomized trial of fixed-dose Rifater for pulmonary tuberculosis	n=105	Fixed dose combination with Rifater vs. isoniazid, rifampin, ethambutol, and purazinamide as separate formulations	In comparing the fixed-dose Rifater (FDC) with therapy of four separate ingredients in the treatment of newly diagnosed smear-positive pulmonary tuberculosis: • Among the patients with a drug susceptibility test result available, four in the FDC group had bacilli resistant to pyrazinamide. In the separate regimen group, two patients had bacilli resistant to ethambutol and six had bacilli resistant to pyrazinamide. • The two regimens were of similar effectiveness with regard to sputum conversion, compliance and radiological improvement. • No patient with FDC treatment developed gastointestinal symptoms, visual disturbance or peripheral neuropathy ($P < 0.05$). • However, FDC treatment resulted in drug-induced fever in one patient. • One patient (3.8%) in the FDC group relapsed 5 months after completing treatment. • Summary: This study suggests that the two regimens had similar effectiveness in the treatment of smear-positive pulmonary tuberculosis.
Teo SK.[30] Randomized, controlled study too assess the combined preparation of isoniazid, rifampicin, and pyrazinamide (Rifater)	n=310	Five-year follow-up of therapy with isoniazid, rifampicin and pyrazinamide (Rifater)	In assessing the acceptability, efficacy, and relapse rate of a combined formulation for tuberculosis treatment, given in three 6-month regimens: • Of 271 patients with drug-sensitive strains who had completed treatment without interruption, sputum cultures converted in all patients. • At the end of 5 years, there were 15 relapses: three (2.2%) in the separate drugs group and 12 (9.3%) in the Rifater group. • Exclusion of two cases in the Rifater group, one with silicotuberculosis and another with no bacteriological confirmation of diagnosis, gave a relapse rate of 7.9% ($P = 0.03$ for the comparison of relapse rates in the two groups). • A combined formulation of three drugs given daily in the initial phase of 6-month short-course therapy, followed by intermittent treatment with isoniazid and rifampicin given three times a week under direct observation for all patients, appears to be less effective than treatment with the component drugs given as separate formulations.

Macnab MF, et al.[31] Evaluation of the 3-drug combination (Rifater) vs. 4-drug therapy in the ambulatory treatment of tuberculosis	n=106	Rifater vs. isoniazid, rifampicin, pyrazinamide and ethambutol	This prospective study tested the subjective impression that use of the combination Rifater was causing delayed sputum conversion and increased drug resistance: • Adults in the Cape Town municipal area with a first episode of pulmonary tuberculosis were treated either with Rifater or a regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. • All patients who took the treatment as prescribed (67 Rifater, 39 the 4-drug regimen) converted to a negative sputum culture by the time 90 doses had been taken. • The rates of inadequate compliance and of side-effects were similar in the two groups. • Drug sensitivity testing of bacteria cultured from pre-treatment sputum specimens revealed an overall primary resistance rate of 4.84% in the population studied, sufficiently low to preclude any necessity for routine pre-treatment drug sensitivity testing.
Am Rev Respir Dis[32] Randomized study	n=310	Daily chemotherapy consisting of: streptomycin, isoniazid, rifampin, and pyrazinamide (1) for 2 months (2SHRZ), (2) for 1 month (1SHRZ), or (3) for 2 months without streptomycin (2HRZ). This was followed for all patients by three times weekly isoniazid and rifampin to a total duration of 6 months	In evaluating a daily combined preparation of isoniazid, rifampin, and pyrazinamide for smear-positive pulmonary tuberculosis: • During the initial period of daily chemotherapy the patients were also allocated at random to be given their HRZ either as a combined formulation (Rifater), each tablet containing 50 mg isoniazid, 120 mg rifampin, and 300 mg pyrazinamide, or as three separate drugs. • During the Rifater versus separate drugs comparison the most common spontaneous complaints were of nausea and vomiting, reported by 8% of 155 patients receiving Rifater and 7% of 155 separate drugs. • Other adverse effects were also reported in similar proportions • Among 271 patients with drug-susceptible strains of tubercle bacilli pretreatment there were no bacteriologic failures during chemotherapy. • During 18 months of subsequent follow-up bacteriologic relapse occurred in 3 (7%) of 46 2SHRZ, 2 (5%) of 42 1SHRZ, and 3 (8%) of 40 2HRZ patients allocated to Rifater and in 0 of 47 2SHRZ, 1 (2%) of 46 1SHRZ, and 1 (2%) of 44 2HRZ patients allocated to separate drugs. • There was no evidence of therapeutic benefit from continuing SHRZ administration beyond 1 month or from adding streptomycin to HRZ. • The relapse rates were slightly higher in the Rifater series (p = 0.04).

Additional Evidence

Dose Simplification: The prinicipal reason why cures are not achieved with available drug regimens for tuberculosis is patient noncompliance or failure to complete the prescribed regimen. Since shortening the total duration of chemotherapy is a potential means of combating this problem, the American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) currently recommend short-course (minimum of 6 months) chemotherapy regimens as preferred alternatives to more prolonged conventional regimens (18-24 months) for the initial treatment of uncomplicated pulmonary and most cases of extrapulmonary tuberculosis in adults. One study compared treatment of pulmonary tuberculosis with either rifapentine and isoniazid once a week or rifampicin and isoniazid twice a week. In this study, twice weekly therapy was more effective in regards to failure/relapse rates with once weekly therapy.[18]

Stable Therapy: A literature search of Medline did not reveal clinical literature relevant to changing therapies once stabilized on an antimycobacterial regimen for tuberculosis. However, one study comparing atovaquone with dapsone for the prevention of *Pneumocystic carinii* pneumonia in patients with HIV infection found that in patients who were receiving dapsone therapy at baseline, significantly more patients in the atovaquone group discontinued therapy due to adverse effects compared with those patients continuing dapsone therapy.[27]

Impact on Physician Visits: The CDC recommends that directly observed therapy (DOT) be used whenever possible to ensure compliance. Therefore, any methods to decrease number of visits, such as short-course chemotherapy regimens will impact physician visits. However, a literature search of Medline did not reveal clinical literature relevant to use of the antimycobacterials and their impact on physician visits.

IX. Conclusions

There is limited clinical efficacy data available for the fixed-dose combination antimycobacterials. Neither agent is available as a generic formulation. The clinical studies presented above do not suggest a clinical benefit in the use of the fixed-dose agents versus use of the separate entity drugs.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant advantage over other alternatives in general use.

X. Recommendations

No brand combination antimycobacterial agent is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Anti-influenza Agents
AHFS 081804, 081828
January 26, 2005

Important Note on the Anti-viral class: The anti-influenza agents, a sub class of anti-viral therapies, as well as the other antiviral agents (interferons, nucleosides and nucleotides, and misc. antivirals), are subject to the Alabama Medicaid Preferred Drug List. However, per Alabama ACT #2003-297, anti-retrovirals are excluded from review for the Preferred Drug List.

I. Overview

Influenza occurs at epidemic rates each year and is the leading cause of respiratory illness in the United States with the majority of complications, hospitalizations, and deaths occurring in the elderly. Vaccination has been the cornerstone for prophylaxis and is recommended annually for immunocompromised persons and those with comorbidities such as chronic pulmonary, cardiovascular, and chronic metabolic diseases.[17] Illness due to influenza in the general population results in increased time off from work and loss of productivity. Recognition of the clinical and economic impact of influenza worldwide has resulted in increased research for alternative methods of prevention and treatment.

Pharmacological interventions have been developed to specifically target viral proteins that facilitate influenza infection of the host. The two classes of antiviral influenza agents are ion channel inhibitors and neuraminidase inhibitors. The ion channel inhibitors, amantadine and rimantadine, inhibit M2 protein which allows hydrogen ions to enter into the cell resulting in the acidification needed for viral replication. The neuraminidase inhibitors, oseltamivir and zanamivir, inhibit viral neuraminidase necessary for aggregation of viral particles.[16] Amantadine was first introduced into the market in 1966 for the treatment of influenza A. Ten years later, amantadine also gained FDA approval for chemoprophylaxis of influenza. Rimantadine, pharmacologically related to amantadine, was marketed in 1993. Although trials have shown clinical efficacy of ion channel inhibitors, *Monto et al* reports that the use of these agents have been limited due to the concern for resistance and the need to ensure that the virus being treated is caused by influenza A.[21] *Hayden et al* further explains that oral rimantadine may be preferable to amantadine for treating influenza A virus infections due to its therapeutic efficacy combined with its lower potential for central nervous system (CNS) side effects.[20] The neuraminidase inhibitors, oseltamivir and zanamivir, both introduced in 1999, are FDA approved to treat influenza A and B. Zanamivir, however is the only antiviral that is not FDA approved for chemoprophylaxis. Caution should be exercised when using zanamivir because it has been associated with brochospasms in patients with a history of airway disease.[4] Clinical studies, such as the IMPACT trial, have shown improved effectiveness in the treatment of influenza when oseltamivir and zanamivir were initiated = 48 hours after the onset of symptoms.[1-7,18] Specific dosage recommendations and precautions must be considered when using ion channel and neuraminidase inhibitors in children, elderly and patients with renal and hepatic impairment. Further study is needed to provide rationale for use of these agents in immunocompromised patients; however, the antiviral influenza agents may be considered in this patient population.[1,4,9,23] This review encompasses all dosage forms and strengths.

Table 1. Anti-influenza agents in this Review

Generic Name	Formulation	Example Brand Name
Amantadine**	100mg capsules, tablets, 50mg/5ml syrup	*Symmetrel
Oseltamivir	75mg capsules, 12mg/ml powder for oral suspension	Tamiflu
Rimantadine	100mg tablets, 50mg/5ml syrup	*Flumadine
Zanamivir	Powder for oral inhaler (Rotadisk) 5mg/blister	Relenza

*Generic Available.
**Amantadine is classified by AHFS as a misc. central nervous system agent (AHFS 289200) and as an anti-infective adamantane (AHFS 081804). This review is all-inclusive of amantadines uses, with emphasis on anti-infective properties.

II. Evidence-Based Medicine and Current Treatment Guidelines[23]

In 2004, the Centers for Disease Control and Prevention issued a document created by the Advisory Committee on Immunization Practices (ACIP) entitled "Prevention and Control of Influenza." This document states, "the primary option for reducing the effect of influenza is immunoprophylaxis with vaccinations." But, even under the best circumstances influenza outbreaks occur. Therefore, antiviral drugs used for chemoprophylaxis or treatment of influenza are key components to controlling morbidity, mortality, and spreading of the disease.

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day, compared with placebo. The medications in this class should also be considered for treatment or chemoprophylaxis in persons at high risk for complications of influenza.[8]

Data are limited regarding the effectiveness of the four antiviral agents in preventing serious influenza-related complications. Evidence for the effectiveness of the four antiviral drugs in this category is based on studies of patients with uncomplicated influenza. Data are also limited and inconclusive concerning the effectiveness of these drugs among persons at high risk for serious complications of influenza and even fewer studies have been conducted addressing the efficacy among pediatric populations (especially in children less than 1 year of age). Rimantadine was approved in 1993 for treatment and chemoprophylaxis of influenza A infection among adults and prophylaxis among children. Although rimantadine is approved only for chemoprophylaxis of influenza A infection among children, certain specialists in the management of influenza consider it appropriate for treatment of influenza A among children.

Chemoprophylactic drugs are not a substitute for vaccination but are critical adjuncts in preventing and controlling influenza. Both amantadine and rimantadine are indicated for prophylaxis of influenza A, but not B. Effectiveness of both drugs is approximately 70-90%. Between the neuraminidase inhibitor antivirals, zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but studies indicate that both drugs are similarly effective in preventing influenza. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak-control programs, which can limit the spread of influenza within chronic care institutions.

Both antiviral agents have also been reported to prevent influenza illness among persons administered chemoprophylaxis after a household member was diagnosed with influenza. Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes. One 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness. Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine. Data are not available regarding the efficacy of any of the four antiviral agents in

preventing influenza among severely immunocompromised persons. Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, development of antibodies in adults after vaccination takes approximately 2 weeks. When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (e.g., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

Updated CDC Guidelines and Recommendations: Influenza Antiviral Medications 2004-05

In the setting of a current influenza vaccine shortage, the CDC has developed interim recommendations on the use of antiviral medications for the 2004-05 influenza season.[32] There are four medications available (as listed in Table 1), although according to the CDC, supplies of zanamivir are limited. When used for treatment within the first two days of illness, all four antiviral medications are similarly effective in reducing the duration of illness by one or two days. Only three medications (amantadine, rimantadine, and oseltamivir) are approved for chemoprophylaxis of influenza. Additionally, local availability and supplies of these medications may vary from community to community, which may impact how these agents are used.

The antiviral medication usage guidelines are highlighted below:

- CDC encourages the use of amantadine or rimantadine for chemoprophylaxis and the use of oseltamivir or zanamivir for treatment as supplies allow, in part to minimize the development of amantadine resistance among circulating influenza viruses.
- People at high risk of serious complications from influenza may benefit most from antiviral medications. Therefore, in general, people who fall into these high risk groups should be given priority for use of influenza antiviral medications:
    - Any person experiencing a potentially life-threatening influenza-related illness should be treated with antiviral medications.
    - Any person at high risk for serious complications of influenza and who is within the first 2 days of illness onset should be treated with antiviral medications. Pregnant women should consult their primary provider regarding use of influenza antiviral medications.
- Antiviral use in children: Rimantadine is approved for prophylaxis of influenza among children aged = 1 year and for treatment and prophylaxis of influenza among adults. Although rimantadine is approved only for prophylaxis of influenza among children, certain specialists in the management of influenza consider it appropriate for treatment of influenza among children. Also available for treatment of children are amantadine (children aged =1 year), oseltamivir (children aged =1 year), or zanamivir (children aged = 7 years).
- All persons who live or work in institutions caring for people at high risk of serious complications of influenza infection should be given antiviral medications in the event of an institutional outbreak.
- All persons at high risk of serious influenza complications should be given antiviral medications if they are likely to be exposed to others infected with influenza.
- Antiviral medications can be considered in other situations when the available supply of such medication is locally adequate. Chemoprophylaxis of persons in communities where influenza viruses are circulating, which typically lasts for 6-8 weeks.
    - Persons at high risk of serious complications who are not able to get vaccinated.
    - Persons at high risk of serious complications who have been vaccinated but have not had time to mount an immune response to the vaccine. In adults, chemoprophylaxis should occur for a period of 2 weeks after vaccination. In children, aged <9 years, chemoprophylaxis should occur for 6 weeks after the first dose, or 2 weeks after the second dose,

depending on whether the child is scheduled to receive one or two doses of vaccine.
  - Persons with immunosuppressive conditions who are not expected to mount an adequate antibody response to influenza vaccine.
  - Healthcare workers with direct patient care responsibilities who are not able to obain vaccine.
  - Treatment of infected adults and children aged >1 year who do not have conditions placing them at high risk for serious complications secondary to influenza infection.

- Where supplies of both influenza vaccine and influenza antiviral medications may not be sufficient to meet demand, the CDC does not recommend the use of influenza antiviral medications for chemoprophylaxis of non-high risk persons in the community.

III. Comparative Indications of the Anti-influenza Agents

Table 2. FDA-Approved Indications for the Anti-influenza Agents

	Oseltamivir	Amantadine	Rimantadine	Zanamivir
FDA-Approved Indications[1-7]	• Treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic = 2 days • Prophylaxis of influenza infection in adults and adolescents = 13 years of age	• Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus • Treatment of parkinsonism • Treatment of drug-induced extrapyramidal reactions	Prophylaxis (adults and children > 1 year of age) and treatment (adults) of illness caused by various strains of influenza A virus	• Treatment of uncomplicated acute illness due to influenza A and B virus in adults and children = 7 years of age who have been symptomatic for = 2 days. • Zanamivir is NOT recommended for treatment of patients with underlying airways disease (such as asthma or chronic obstructive pulmonary disease)

IV. Pharmacokinetic Parameters of the Anti-influenza Agents

Table 3. Pharmacokinetic Parameters of the Anti-influenza Agents

	Oseltamivir	Amantadine	Rimantadine	Zanamivir
Mechanism of Action [1-7,23]	Oseltamivir inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.	Amantadine's antiviral activity is not completely understood. It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein.	The mechanism of action is not fully understood. It appears to exert its inhibitory effect early in the viral replicative cycle, possibly inhibiting the uncoating of the virus.	Zanamivir inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.
Pharmacokinetics [1-7,23]				
Bioavailability	75% as oseltamivir carboxylate < 5% as oseltamivir	86-94%	100%	4% -25%
Protein binding	Oseltamivir carboxylate 3% Oseltamivir 42%	~67%	~40%	< 10%
Metabolism	Hepatic, 90% to oseltamivir carboxylate.	Not appreciable	Extensively hepatic	None
Active Metabolites	Oseltamivir carboxylate	Not appreciable	Not appreciable	None
Elimination Half-Life (hrs)	>99% (Renal) Oseltamivir carboxylate 6-10 Oseltamivir 1-3	80-90% (Renal) 10-25	< 25% unchanged (Renal) 25	Renal 2 -5

V. Drug Interactions of the Anti-influenza Agents

There are no level 1 (most severe and life-threatening) drug interactions with the anti-influenza agents in this class.[6]

Table 4. Drug Interactions of the Anti-influenza Agents

	Oseltamivir	Amantadine (All interactions level 4)	Rimantadine (All interactions level 5)	Zanamivir
Drug Interactions [1-7,23]	• No clinically significant pharmacokinetic drug interactions are predicted.	• Careful observation is required when amantadine is administered concurrently with central nervous system stimulants. • Agents with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine. • Coadministration of thioridazine may worsen tremor in Parkinson's disease. • Coadministration of triamterene thiazide diuretics resulted in a higher plasma amantadine concentration. • Coadministration of trimethoprim-sulfamethoxazole may impair renal clearance of amantadine resulting in higher plasma concentrations. • Coadministration of quinine or quinidine with amantadine was shown to reduce the renal clearance of amantadine.	• When a single 100 mg dose of rimantadine was administered 1 hour after cimetidine (300 mg 4 times/day) in healthy adults, the apparent total rimantadine clearance was reduced by 18%. • Coadministration with acetaminophen reduced the peak concentration and AUC values for rimantadine by 11%. • Peak plasma concentrations and AUC of rimantadine were reduced by 10% when coadministered with aspirin.	• No clinically significant pharmacokinetic drug interactions are predicted.

VI. Adverse Drug Events of the Anti-influenza Agents

Side Effects and Adverse Reactions

When considering the use of influenza antiviral medications (e.g., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function; presence of other medical conditions; indications for use (e.g., prophylaxis or therapy); and the potential for interaction with other medications.[23] Rimantadine and amantadine have comparable efficacy in prevention and treatment on influenza A, although rimantadine induces fewer adverse effects than amantadine.[24]

Table 5. Common Adverse Events (%) Reported for the Anti-influenza Agents

Treatment Group	Oseltamivir Tamiflu® (Placebo) N = 724 (716)	Amantadine Symmetrel®	Rimantadine Flumadine® (Placebo) n = 1027 (986)	Zanamivir Relenza® (Placebo) n = 1132 (1520)
Adverse Events (%)[1-7]				
Body as a Whole				
Abdominal Pain	2.2 (2.2)		1.4 (0.8)	
Fatigue	1.0 (1.0)	v	1.0 (0.9)	
Asthenia			1.4 (0.5)	
Cardiovascular				
Peripheral edema		v		
Orthostatic hypotension		v		
Central Nervous System				
Dizziness	2.1 (3.5)	v	1.9 (1.1)	2 (<1)
Headache	1.8 (2.0)	v	1.4 (1.3)	2 (3)
Vertigo	1.0 (0.6)			
Insomnia	1.1 (0.8)	v	2.1 (0.9)	
Nervousness		v	1.3 (0.6)	
Depression		v		
Lightheadedness		v		
Irritability		v		
Ataxia		v		
Hallucinations		v		
Anxiety		v		
Dermatologic				
Livedo reticularis		v		
Gastrointestinal				
Diarrhea	6.6 (9.8)	v		3.0 (4.0)
Nausea	9.9 (5.6)	v	2.8 (1.6)	3.0 (3.0)
Vomiting	9.4 (2.9)	v	1.7 (0.6)	1.0 (2.0)
Anorexia		v	1.6 (0.8)	
Dry Mouth		v	1.5 (0.6)	
Abdominal Pain			1.4 (0.8)	
Respiratory				
Bronchitis	2.3 (2.1)			2.0 (3.0)
Cough	1.2 (1.7)			2.0 (3.0)
Nasal signs and symptoms				2.0 (3.0)
Sinusitis				3.0 (2.0)
Dyspnea				
Ear, nose, and throat infections				2.0 (2.0)
Dry nose		v		
Other				
Peripheral edema		v		

v = reported but incidence unknown.

Prophylaxis Group	**Oseltamivir Tamiflu® (Placebo) n =1480 (1434)**	**Amantadine Symmetrel® (Placebo) n =148 (143)**	**Rimantadine Flumadine® (Placebo) n = 145 (143)**	**Zanamivir Relenza® (Placebo) n =1132 (1520)**
Adverse Events (%)[1-7]				
Body as a Whole				
Fatigue	7.9 (7.5)			
Central Nervous System				
Dizziness	1.6 (1.5)	2.1 (0)	0.7 (0)	
Headache	20.1 (17.5)			
Vertigo	0.3 (0.2)			
Insomnia	1.2 (1.2)	7.0 (0.7)	3.4 (0.7)	
Nervousness		2.8 (0.7)	2.1 (0.7)	
Impaired Concentration		2.1 (1.4)	2.1 (1.4)	
Depression		3.5 (0.7)	0.7 (0.7)	
Gastrointestinal				
Diarrhea	3.2 (2.6)			
Nausea	7.0 (3.9)			
Vomiting	2.1 (1.0)			
Anorexia				
Abdominal Pain	2.0 (1.6)			
Respiratory				
Bronchitis	0.7 (1.2)			

Pediatric Treatment	**Oseltamivir Tamiflu® (Placebo) n = 515 (517)**	**Amantadine Symmetrel®**	**Rimantadine Flumadine®**	**Zanamivir Relenza® (Placebo)**
Adverse Events (%)[1-7]				
Body as a Whole				
Lymphadenopathy	1.0 (1.5)			
Dermatologic				
Dermatitis	1.0 (1.9)			
Gastrointestinal				
Diarrhea	9.5 (10.6)			2.0 (2.0)
Nausea	3.3 (4.3)			<1 (2.0)
Vomiting	15.0 (9.3)			2.0 (3.0)
Abdominal Pain	4.7 (3.9)			
Hematologic				
Epistaxis	3.1 (2.5)			
Ocular				
Conjunctivitis	1.0 (0.4)			
Respiratory				
Bronchitis	1.6 (2.1)			
Cough				<1 (2.0)
Nasal signs and symptoms				
Sinusitis	1.7 (2.5)			
Asthma	3.5 (3.7)			<1 (2.0)
Pneumonia	1.9 (3.3)			
Otitis media	8.7 (11.2)			
Ear Disorder	1.7 (1.2)			
Tympanic membrane Disorder	1.0 (1.2)			
Ear, nose, throat infection				5.0 (5.0)
Ear, nose, throat hemorrhage				<1 (2.0)

Seizure Disorders [23]

Amantadine- An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine. Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine- Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine. The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir- Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use. [23]

VII. Dosing and Administration for the Anti-influenza Agents

Table 6. Dosing for the Anti-influenza Agents

	Oseltamivir	Amantadine	Rimantadine	Zanamivir
Usual Adult Daily Dose[1-7,23]	**Treatment of influenza:** 75 mg twice daily for 5 days **Prophylaxis of influenza during community outbreak** 5 mg QD up to 6 weeks **Prophylaxis of influenza following exposure:** 75 mg QD for = 7 days	**Treatment of influenza:** 200 MG QD or 100 MG BID for 3-5 days **Prophylaxis of influenza:** 200 mg QD or 100 mg BID minimum 10 day course	**Treatment of influenza:** 100 MG BID for 7 days **Prophylaxis of influenza:** 100 mg BID for 7 days	**Treatment of Influenza:** 2 inhalations (10 mg) BID for 5 days
Usual Child Daily Dose[1-7,23]	**Treatment of influenza:** ≥ 1 up-By weight 15kg or less-30mg BID Over 15-23kg-45mg BID Over 23-40kg-60mg BID Over 40kg- 75mg BID ≥ 13 y/o-75mg BID **Prophylaxis** ≥ 13 y/o-75mg daily	**Treatment of influenza:** Age 1-9- 4.4-8.8mg/kg body weight/day. Do not exceed 150mg/day. ≥ 10 y/o -200mg/day (100mg BID) *Children weighing less than 40kg-5mg/kg body weight/day regardless of age. **Prophylaxis** Age 1-9- 4.4-8.8mg/kg body weight/day. Do not exceed 150mg/day. ≥ 10 y/o-200mg/day (100mg BID) *Children weighing less than 40kg-5mg/kg body weight/day regardless of age.	**Treatment of influenza:** Not FDA approved **Prophylaxis** Age 1-9-5mg/kg body weight/day (1 or 2 doses) ≥ 10 y/o-200mg/day (100mg BID) *Children weigh ing less than 40kg-5mg/kg body weight/day regardless of age.	**Treatment of influenza:** Children ≥ 7 -Two 5mg inhalations BID
Dosing for ≥65 and over[1-7,23]	**No reduction required on age alone.**	**Prophylaxis** 100mg daily	**Treatment of influenza:** Consider reducing to 100mg daily if adverse effects are experienced. **Prophylaxis** 100mg/day	**No reduction required on age alone.**
Pregnancy Category[1-7] *	C	C	C	C
Use in Lactation[1-7]	• It is not known whether oseltamivir and oseltamivir carboxylate are excreted in human milk. • Oseltamivir should only be used if the	Amantadine is excreted in breast milk. Use is not recommended in nursing mothers.	Do not administer rimantadine to nursing mothers because of the adverse effects noted in	It is not known whether zanamivir is excreted in human milk. Caution should be exercised when administering to nursing mother.

	Oseltamivir	Amantadine	Rimantadine	Zanamivir
	potential benefit for the lactating mothers justifies the potential risk to the breast-fed infant.		offspring of rats treated with rimantadine during the nursing period.	
Persons with impaired renal function[23]	For patients with creatinine clearance of 10--30 mL/min, a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the prophylaxis dosage to 75 mg every other day is recommended.	A reduction in dosage is recommended for patients with creatinine clearance $\leq$ 50 mL/min/1.73m^2.	A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance < 10 mL/min.	Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Therefore, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild to moderate or severe impairment in renal function .
Availability[1-7]	• 75 MG capsules • 12 MG/ML powder for oral suspension	• 100 MG tablets, capsules • 50 MG/5 ML syrup	• 100 MG tablets • 50 MG/5 ML syrup	Rotadisk containing 4 blisters. Each blister contains 5mg of drug.
Warnings and Precautions[1-7]	• Efficacy of oseltamivir in patients who begin treatment after 40 hours of symptoms has not been established. • There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza virus types A and B. • Safety and efficacy of repeated treatment or prophylaxis courses have not been studied. • Efficacy for treatment or prophylaxis courses has not been established in immunocompromised patients. • Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Oseltamivir has not been shown to prevent such complications. • The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated. • Dose adjustment is recommended for patients with a serum creatinine clearance < 30 ml/min.	• Deaths have been reported from overdose with amantadine. The lowest reported acute lethal dose was 1 gram. • Suicide attempts and suicide ideation have been reported in patients with and without prior history of psychiatric disorders. • Closely observe patients with a history of epilepsy or other seizures for increased seizure activity. • Patients who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness and adequate motor coordination are important. • Patients with a history of congestive heart failure or peripheral edema should be followed as there are patients who developed congestive heart failure while receiving amantadine. • Because amantadine has anticholinergic effects and may cause	• An increased incidence of seizures has been reported in patients with a seizure history. • Safety and efficacy of rimantadine in children have not been established for the treatment of symptomatic influenza infection. • There is the potential for accumulation of rimantadine and its metabolites in plasma; there fore, caution should be exercised in patients with renal or hepatic insufficiency and in the treatment of symptomatic influenza infection. • Influenza A virus strains resistant to rimantadine can emerge	• Brochospasms and decline in lung function have been reported. Zanamivir is not recommended for treatment of patients with underlying airway disease. • Zanamivir should be discontinued in any patient who develops bronchospasm or decline in respiratory function. • Patients should be instructed in the use of the delivery system. • There is no evidence for efficacy in any illness caused by agents other than influenza virus A and B. • No data are available to support safety and efficacy in patients who begin treatment after 48 hours of symptoms. • Allergic-like reactions, including oropharyngeal edema and serious skin rashes have been reported. • Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. • Use should not affect the evaluation of

	Oseltamivir	Amantadine	Rimantadine	Zanamivir
	• The efficacy and safety in children < 1 year of age have not been established. • Use should not affect the evaluation of individuals for annual influenza vaccination in accordance with the guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.	mydriasis, it should not be given to patients with untreated angle closure glaucoma. • The dose of anticholinergic drugs or of amantadine should be reduced if atropine-like effects appear when these drugs are used concurrently. • Sporadic cases of neuroleptic malignant syndrome have been reported in association with dose reduction or withdrawal of amantadine therapy. • The dose of amantadine should be reduced in renally impaired patients and in individuals who are 65 years of age or older. • Caution should be exercised when administering amantadine to patients with liver disease. • Caution should be exercised when administering amantadine to patients with a history of recurrent eczematoid rash or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents.	during treatment and such resistant strains have been shown to be transmissible and cause typical influenza illness. • Early vaccination on an annual basis as recommended by the Centers for Disease control on Immunization Practices Advisory Committee is the method of choice in the prophylaxis of influenza unless vaccination is contraindicated, not available, or not feasible.	individuals for annual influenza vaccination in accordance with the guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. • No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

***Pregnancy**

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.[23]

VIII. Comparative Effectiveness of the Anti-influenza Agents

Table 7. Comparative Clinical Efficacy and Safety of the Antiviral Influenza Agents

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
Treanor J et al. [9] 2000	Randomized, double blind, placebo controlled, multicenter study	• Adults aged 18 to 65 years • Present within 36 hours of onset of influenza symptoms • Oral temperature of 38ºC or higher • Plus 1 or more respiratory symptoms including cough, sore throat nasal symptoms • 1 or more constitutional symptoms including headache, malaise, myalgia, sweats and/or chills or fatigue • Women required to have a negative urine pregnancy test	629	• Oseltamivir 75mg BID for 5 days or • 150mg BID for 5 days or • Placebo for 5 days • Participants were instructed to use acetaminophen for symptom relief PRN	21 days	**Primary Endpoints** Time to resolution of illness ***Other Endpoints*** • Duration and severity of individual symptoms • Incidence of secondary complications • Quantity of viral shedding **Efficacy: oseltamivir>placebo** • The duration of illness in which the symptoms were rated as mild or less were, 103.3 hours (4.3 days) in the placebo group, 71.5 hours (3.0 days) and 69.9 hours (2.9 days) in the 75mg, and 150mg groups respectively. • Treatment with oseltamivir at either 75 or 150mg twice daily resulted in statistically significant reductions ($p < 0.001$ and $p = 0.006$, respectively) in the symptom score AUC which reflects the severity and duration of illness. There were no differences between the 2 doses of oseltamivir with regard to effects. • Oseltamivir treatment reduced median duration of illness by more than 30% ($p = 0.006$) and median severity of illness by 40% ($p < 0.001$). • Duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours (43% reduction) in the 75mg group and to 40 hours (27% reduction) in the 150mg group. • The duration of myalgia was also reduced, from a median of 28 hours in placebo recipients to 16 hours (42% reduction) in the 75mg group and 19 hours (32% reduction) in the 150mg group.

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						• The percentage of subjects with fever at 24 hours was 39% in the placebo group, compared with 26% in the 75mg group (13% difference; 95% CI, 25%-2 %) and 21% in the 150mg group (18% difference; 95% CI, 29%-6%). • After 24 hours of treatment, median viral titers had decreased by 1.2 logs in the placebo group vs. 1.7 and 2.0 logs in the 75mg and 150mg oseltamivir groups, respectively. These differences were not statistically significant. **Safety: *placebo > oseltamivir*** • Discontinue rate during therapy was 3% in the placebo group, 1.5% in the 75mg group, and 2% in the 150mg group. • 1 participant from the oseltamivir 150-mg group withdrew prematurely because of gastrointestinal events. • Upper gastrointestinal side effects (nausea or nausea with vomiting) were reported more frequently in those receiving oseltamivir. For nausea, these rates were 7.4% (15/204) for placebo, 17% (35/205) for recipients of 75mg oseltamivir and 19% (39/205) for recipients of 150mg oseltamivir. Overall difference in the 3 groups, p =0.002; differences between placebo and 75-mg and 150-mg oseltamivir, p = 0.002 and p < 0.001, respectively. • For vomiting, the rates were 3.4% (7/204) with placebo, 13.1% (27/206) with 75mg oseltamivir and 15.1% (31/205) with 150mg oseltamivir. (p < 0.001 for overall difference in the 3 groups and differences between placebo and 75mg and 150mg oseltamivir).

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
Welliver, R et al. [10] 2001	Cluster-randomized, double-blind, placebo-controlled	• Households with a minimum of 2 and a maximum of 8 contacts • < 48 hours of symptom onset in a index case • Index case child or children >12 years of age • Household members with well-controlled comorbidities including those who were vaccinated • Elderly Patients > 65 years of age with mental status questionnaire score of 7 or higher	377	• Oseltamivir 75mg QD for 7 days or • Placebo QD for 7 days • 500mg of acetaminophen was provided for symptom relief PRN	7 days	**Primary Endpoints** Proportion of contacts of an influenza-positive IC (indexcases) with laboratory-confirmed clinical influenza during the dosing period (protective efficacy). ***Other Endpoints*** Number of households with additional influenza-related illnesses **Efficacy: oseltamivir > placebo** • Protective efficacy of oseltamivir determined on the basis of the number of individuals and households exposed to all ICs was high at 89% for individuals (95% CI, 71%-96%; p<0.001) and 86% for households (95% CI, 60%-95%; p<0.001). • High protective efficacy was demonstrated in contacts of infected ICs where the incidence of laboratory –confirmed clinical influenza in individuals and household contacts receiving oseltamivir during the 7-day prophylaxis period was reduced by 89% (95% CI, 67%-97%; p<0.001) and 84% (95% CI, 49%-95%; p<0.001), respectively • Protective efficacy for individuals exposed to influenza outside the household was 89% (95% CI, 10%- 99%; p =0.009). • Twenty-one of the clinical cases among the placebo recipients were infected with influenza A and 13 with influenza B virus. None of the clinical cases in the group of oseltamivir-treated contacts was infected with influenza A virus. The protective efficacy against influenza B illness in contacts of all ICs was 78.5% (p=0.02). • Frequency of individuals shedding virus and therefore more likely to transmit to others was

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						significantly reduced in oseltamivir recipients compared with placebo. The protective efficacy in contacts of an influenza positive IC was 84% (95% CI, 57%-95%; p<0.001). **Safety: placebo = oseltamivir** • Withdrawal rates due to adverse events were low in both groups: 1% receiving oseltamivir and 0.4% receiving placebo. • Gastrointestinal tract effects were reported with similar frequency in recipients of oseltamivir (9.3% [46/494]) and placebo (7.2% [33/461]). • Nausea reported by 5.5% (27/494) of oseltamivir and 2.6% (12/461) of placebo recipients was mild and transient.
Reuman P et al. [11] 1989	Two double-blind, placebo controlled, randomized	*Naturally occurring influenza study:* • Subjects aged 18 to 55 years *Experimental challenge study*: • Subjects aged 18-40 years from college student population and • Serum HAI titer = 1:8 for influenza A	476/ 78	*Naturally occurring influenza study*: • Amantadine 100mg QD or • 200mg QD • Placebo *Experimental challenge study*: • Placebo • Amantadine 50mg QD • Amantadine 100mg QD • Amantadine 200mg QD	6 weeks/13 days	**Primary Endpoints** • Evaluation of HAI antibody to the three prevalent strains H1N1, H3N2 and B • Positive viral assays • Positive amantadine blood levels **Efficacy: amantadine > placebo** *Naturally occurring influenza study*: • Of the 158 subjects in the placebo group, only 8/158 subjects (5%) were confirmed to be infected with influenza A or B. This rate was far below the pre-study estimated infection rate of 30% used in calculating the size of the study needed to make a valid statistical comparisons. • Random blood sampling done on 48 subjects showed that 30 samples from the amantadine group were positive for drug and all 18 samples from the placebo group were negative for drug. • *Experimental challenge study*:

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						• Influenza illness was found in 11 of 19 (58%) placebo subjects given 50 mg/day amantadine, 3 of 20 (15%) subjects given 100mg/day amantadine and in 2 of 19 (11%) subjects given 200 mg/day amantadine (compared with placebo: • P = 0.017, 0.006, and 0.003, respectively). • Amantadine at all doses significantly ($p < 0.05$) suppressed respiratory symptoms on days 2 through 6 post–challenge and systemic symptoms on days 2 and 3 post-challenge. • The placebo group had significantly higher ($p < 0.05$) mean viral titers than any amantadine group on each days 1 through 6 post-challenge. • Increases in HAI antibody titers (= 4-fold) following viral challenge were seen in 13 (68%) of 19 placebo subjects and in 23 (39%) subjects receiving amantadine ($p=0.03$). • Mean serum amantadine levels were significantly different between groups at each time ($p<0.001$) increasing approximately 2–fold for each dose increase. **Safety: placebo = amantadine 100mg > amantadine 200mg** *Naturally occurring influenza study*: • The percentage of patients with adverse experiences did not differ between the placebo (31%) and 100mg treatment groups (30%). • A significantly greater number of total adverse experiences ($p = 0.009$) and CNS related adverse events (sleep disturbances, nervousness and dizziness) ($p<0.001$) were observed in the amantadine 200mg group compared to the placebo group. • The individual symptoms of dry nose and dry

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						mouth were significantly greater (p = 0.005) in the 200mg treatment group compared to the other treatment groups. • Three subjects withdrew because of an adverse experience: one in the placebo group and two in the 200mg group. • *Experimental challenge study:* • There were no significant differences in the percent of subjects with at least one adverse experience between the treatment groups pre-challenge (p = 0.42) and post-challenge (p =0.20). • However, the number of CNS adverse experiences was found to significantly correlate with amantadine blood levels obtained prior to challenge 2 h after the first dose (p =0.035). Amantadine blood levels were higher in subjects reporting more CNS adverse experiences.
Monto, S et al. [12] 1995	Double-blind, placebo controlled randomized	• Nursing home patients with or without previous vaccination • Patients without significant renal or hepatic impairment • Patients without chronic conditions that put them at risk for complications	328	• Rimantadine 100mg QD or • Rimantadine 200mg QD or • Placebo	8 weeks	**Primary Endpoints** • Influenza like illness • Laboratory-confirmed clinical influenza • Influenza virus infection with or without clinical illness **Efficacy: rimantadine 200mg = rimantadine 100mg = placebo** • Rimantadine was most efficacious at reducing the likelihood of clinical illness; the RR were 0.40 (95%CI 0.13-1.25) and 0.43 (95% CI 0.14-1.35) for 100mg and 200mg respectively but was less effective in reducing the likelihood of laboratory-confirmed infection; the RR were 0.50 (95%CI 0.12-2.18) and 0.54 (95% CI, 0.12-2.34) for 100mg and 200mg, respectively. • The efficacy of rimantadine in reducing the likelihood of clinical influenza-like illness was

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						estimated for the groups receiving active prophylaxis combined versus the placebo group. In that analysis, efficacy was estimated to be 58% (P=0.079). • No additional benefit was demonstrated for the 200mg/day dosages over the 100mg/day dosage; most estimates produced nearly identical results. • Influenza A (H3N2) was the only strain identified during this study. **Safety: Placebo > rimantadine 100 mg > rimantadine 200 mg** • The most commonly reported symptom in all groups was confusion (10 to 14%). Nausea (8 to 11%) and loss of appetite (6 to 10%) were also frequently reported. Four (3%) participants in the 200mg/day groups and one (2%) participant in the placebo group experienced a seizure or clonic twitching while receiving study drug or placebo. There were three episodes all at 200mg/day dose. • Participants in the 200mg/day-prophylaxis group were 2.3 times more likely to experience a significant health event than those in the placebo group (p =0.031). • Participants in the 200mg/day group were 1.9 times more likely to withdraw from the study than the placebo group. 31/132 patients withdrew from the 200mg group (p = 0.041). • Increased risk of withdrawal from the study was also observed when comparing the 100mg/day group with the placebo group. 23/130 patients withdrew from the 100mg group (p =0.213). • Dosage reduction to 100mg/day was recommended in elderly due to fewer side effects.

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
Brady, M et al. [13] 1990	Placebo controlled double-blind randomized	• Healthy adult volunteers • 18 to 55 years	228	• Rimantadine 100mg QD for 6 weeks • Placebo QD for 6 weeks	6 weeks	**Primary Endpoints** Isolation of influenza A virus or a fourfold or greater rise in HAI antibody titer to influenza A virus in serum. **Efficacy: rimantadine [3] placebo** • A total of 7 of 112 rimantadine recipients and 20 of 110 placebo recipients developed influenza A virus infection ($p < 0.01$). • Rimantadine recipients developed influenza A illness significantly less often than did placebo recipients (91 of 112 versus 7 of 110 recipients, respectively [$p < 0.04$]). • The efficacy of rimantadine was 86% for prevention of influenza illness and 66% for prevention of influenza A virus infection. **Safety: placebo > rimantadine** • 10 (8.7%) of the 114 rimantadine-treated subjects and 5 (4.4%) of 114 placebo recipients reported one or more clinically adverse experiences. • The most frequently reported adverse experience in both groups was related to the gastrointestinal and central nervous system. The rates of headache and fatigue were similar in both groups.
Campion K et al. [14] 1998 MIST Trial	Randomized double blind placebo controlled	• Healthy individuals • 12 years or older • Presenting with influenza like illness of 36 h duration or less • Patients had to present with fever >37.8º C, feverishness, or both • And two of these	455	• 10mg inhaled zanamivir or • Placebo twice daily for 5 days • Patients received relief medications paracetamol	28 days	**Primary Endpoints** Length of time to alleviation of clinically important symptoms including absence of fever, mild headache, cough, myalgia and sore throat for 24 hours. ***Secondary Endpoints*** • The length of time to return to normal activities • Mean symptom scores, sleep disturbance, use of relief medications, rate of complications and associated use of antibiotics **Efficacy: zanamivir >placebo** • Overall, 321 (71 %) patients had laboratory-

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
		symptoms: myalgia, cough, headache, or sore throat		and pholcodine cough mixture to treat persistent severe symptoms		confirmed influenza. Of these, 214 (67%) had influenza A (H3N2) and 33% had influenza B. • Zanamivir significantly shortened the time to alleviation of symptoms compared with placebo (5.0 vs. 6.5 days P =0.011). This 1.5 day benefit was seen also for influenza positive patients (P =0.004). • In patients who were febrile and received zanamivir symptoms were decreased 2.0 days earlier than in those on placebo (P <0.001) in the intention to treat and influenza positive patient groups. • Influenza positive patients treated with zanamivir had significantly less severe symptoms overall on days 1-14 than those on placebo (P <0.05). • High-risk patients had significantly fewer complications than those on placebo (P =0.004) and fewer high risk patients needed antibiotic medication to treat those complications (P =0.025). • When zanamivir recipients were compared to patients on placebo, return to normal activities, sleep disturbances, complication rates, and associated use of antibiotics were all less in the intention-to-treat and influenza-positive populations, but were not significant. **Safety: placebo ≤ zanamivir** • 83 (37%) patients on zanamivir reported adverse events compared with 98 (43%) of those on placebo. • The most commonly reported events during treatment in the zanamivir group vs placebo was bronchitis (3 vs 5%), cough (4 vs 6%), sinusitis (4 vs 1%), lower-respiratory-tract infections (3 vs

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						3%), diarrhea (1 vs 4%) and nausea or vomiting (2 vs 4%). • High risk patients experienced fewer adverse events than those on placebo (38 vs 56%). Most were respiratory events in nature, with 36% of placebo patients reporting a respiratory event compared with 16 % on zanamivir.
Monto, A et al. [15] 1999	Double-blind randomized placebo controlled	• Healthy adults • 18-69 years	1107	• Zanamivir 10mg by self-activated inhalation • Or placebo with lactose as the base administered by self – activated inhalation	28 days	**Primary Endpoint** • Proportion of randomized subjects who during prophylaxis developed laboratory–confirmed clinical influenza • Effectiveness of zanamivir would be defined by 70% prevention. **Efficacy: zanamivir = placebo** • The odds ratio of the illness frequencies between study groups was 0.31. As shown, this approximates an RR of 0.33 or an efficacy of 67% (95% CI, 39%-83%). • When those illnesses considered were restricted to those with temperatures of at least 37.8º C that were laboratory-confirmed as influenza, the efficacy was 84% (9% CI, 55%-94%). • Influenza infections with or without illness were prevented with a lower efficacy than symptomatic infections of 31% (95% CI, 4%-50%). • When the analysis was restricted to unvaccinated persons, the odds ratio for laboratory –confirmed clinical influenza was 0.38 or 60 % efficacious (CI, 24%-80%; P=0.009). • 14 % of the participants were vaccinated and the vaccine minimally protected against the A (H3N2) virus. At both testing sites, type A was the primary virus isolated.

Reference	Study Design	Entry Criteria	n	Treatment Regimen	Duration of Study	Results
						Safety: placebo = zanamivir • Adverse effects were observed in 5% of the placebo group and 5% of the zanamivir group. • Withdrawals from the trial for any reason occurred in 17 (3%) subjects from the placebo group and 10 (2%) from the zanamivir group; those thought by the participants to be potentially drug related occurred among 7 (1%) and 4 (<1%) subjects in the two groups, respectively.

Additional Evidence

Dose Simplification: The drugs in this class are largely used in acute situations, for limited periods of time (5-10 days). Zanamivir is the only agent available in an inhalation formulation, which can be a limitation for certain patients who may not be able to use the device. At this time, no special release formulations are available that make dosing more convenient for one product over the others in the class. The drugs in this class are given either once or twice daily.

No studies were found that have looked at adherence with the inhalation agent versus oral agents, and any impact on the outcome of the disease. According to a review performed by Schmidt, all of the anti-influenza drugs shorten the course of influenza disease by approximately one day, and relieve symptoms to some extent, but there is still some uncertainty as to whether antiviral therapy leads to a reduction in serious complications and hospitalization.[30]

Stable Therapy: Compared with other anti-influenza agents, the neuraminidase inhibitors are effective for all influenza types and there has been little evidence of the emergence of viral resistance, as has been seen with amantadine.[31]

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical literature relevant to use of the anti-influenza agents and their impact on physician visits.

IX. Conclusion

When used for the treatment of influenza within the first two days of illness, all four antiviral medications are similarly effective in reducing the duration of illness.[32] Rimantadine and amantadine are only active against influenza A virus. The neuraminidase inhibitors are active against both influenza A and B virus and may offer less severe gastrointestinal side effects such as nausea and vomiting. Currently, comparative clinical trials of the efficacy and safety of ion channel inhibitors and neuraminidase inhibitors are limited (no direct comparative studies are published). Only amantadine and rimantadine are available in a generic formulation.

Zanamivir is not indicated for prophylaxis, as the other agents are, but has been studied for this use. Selection of an antiviral agent to prevent or treat influenza should be based on each drug's spectrum of activity, and side effects.[16] Other considerations include zanamivir's availability as an oral powder for inhalation, which may limit its acceptance by some patients. Antiviral agents should not be substituted for the suggested annual influenza vaccine. [1-8, 23] These agents may be used as adjunctive therapy for the prevention and/or treatment of influenza, especially in high risk patients.

The CDC has issued guidelines and recommendations on the use of the antiviral medications for influenza, due to limited availability of the influenza vaccine for the 2004 influenza season. The recommendations encourage the use of amantadine and rimantadine for chemoprophylaxis of influenza, and use of oseltamivir or zanamivir for treatment of influenza, in hopes resistance to amantadine among circulating influenza viruses can be minimized. Utilization and need for these agents may vary from one influenza season to the next, depending on recommendations from the CDC.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use. The Alabama Medicaid Agency may consider evaluating the use of oseltamivir and zanamivir and making these drugs available through medical justification through the prior authorization program, to ensure use primarily for the <u>treatment</u> of influenza, as indicated by the CDC recommendations.

X. Recommendation

No brand anti-influenza agent is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Interferons
AHFS 081820
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I. Overview

The interferons are a group of proteins that are normally produced by cells in response to viral infection and other stimuli.[1] They were first described in 1957, and were named for their ability to interfere with replicating viruses. Natural and man-made interferons are produced to help the immune system fight viral infections and certain cancers. Interferons are used to treat AIDS-related Kaposi's sarcoma, hepatitis B and C, and certain types of cancers.

This review encompasses all dosage forms and strengths. There are no generic formulations available for the drugs in this class.

Table 1. Interferons in this Review

Generic Name	Formulation	Example Brand Name (s)
Interferon alfa-n3	Injection	Alferon N
Interferon alfacon-1	Injection	Infergen
Interferon alfa-2b, Recombinant	Injection	Intron A
Peginterferon alfa-2a	Injection	Pegasys
Peginterferon alfa-2b	Injection	PEG-Intron, PEG-Intron Redipen
Interferon alfa-2a, Recombinant	Injection	Roferon-A

No generic formulations are available for the agents in this class.

II. Evidence Based Medicine and Current Treatment Guidelines

Interferon alfa-2a is a recombinant alpha interferon (IFN). The alpha IFNs include more than 25 subtypes; interferon alfa-2a represents only one specific subtype.[2,3] Alpha and beta IFNs are structurally and functionally related. Interferon alfa-2a is a highly purified protein containing 165 amino acids and is produced by recombinant DNA technology using a genetically engineered *Escherichia coli* bacterium, containing DNA that codes for the protein. Interferon alfa-2a differs from interferon alfa-2b by only one amino acid at position 23.

Studies have shown that interferon alfa-2a can normalize serum ALT, improve liver histology, and reduce viral load in patients with hepatitis C.[3] Other studies have shown that interferon alfa-2a can produce clinical responses or disease stabilization in patients with hairy cell leukemia or AIDS-related Kaposi's sarcoma. In patients with Philadelphia-chromosome positive chronic myelogenous leukemia (CML), interferon alfa-2a in combination with chemotherapy can prolong overall survival and delay disease progression as compared to patients treated with chemotherapy alone. Interferon alfa-2a has achieved sustained complete cytogenetic responses in a small subset of patients with CML in the chronic phase. Interferon alfa-2a has also been studied in the treatment of melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma including cutaneous T-cell lymphoma. Extensive research of the alfa interferons in combination with 5-fluorouracil (5-FU) for the treatment of colorectal cancer has shown no benefit over 5-FU therapy alone.

In 1986, the FDA approved interferon alfa-2a for the treatment of hairy cell leukemia. In September 1999, the FDA oncology advisory panel recommended against approval of interferon alfa-2a (Roferon® A) for the treatment of early-stage melanoma. A long-lasting pegylated formulation of interferon alfa-2a (peginterferon alfa-2a, Pegasys®) has been approved by the FDA (see Peginterferon alfa-2a monograph). In a phase II/III study of hepatitis C patients with cirrhosis, response rates with peginterferon alfa-2a were higher than those seen in patients treated

with standard alpha interferon.[3] For use in the treatment of external condylomata acuminate, 80% of patients treated with interferon alfa-n3 had a complete or partial resolution of genital warts compared to only 44% of those treated with placebo.[3]

Although the drugs in this class can be used for multiple indications, the remainder of this section will focus on the treatment of hepatitis.

Chronic Hepatitis

Hepatitis is a major cause of morbidity and mortality in the United States.[4] Viral hepatitis is the clinically important hepatotrophic viruses responsible for hepatitis A (HAV), hepatitis B (HBV), delta hepatitis (HDV), hepatitis C (HCV), and hepatitis E (HEV).

Around 56,000 cases of hepatitis are reported yearly.[4] It is likely statistics are low due to incomplete reporting, so actual numbers are much higher. Outside the United States, viral hepatitis is a major health problem. The World Health Organization lists HBV as the ninth leading cause of death in the world. Hepatitis C is the most common blood-bourne infection in the United States with a prevalence of at least 1.8% nationwide.[3] End-stage liver disease induced by hepatitis C is the foremost cause of liver transplantation in this country.

Treatment of hepatitis has evolved in the last ten years. The first treatments available were with interferon alone, and had sustained response rates of fewer than 10%.[5] Through investigation of new treatments, ribavirin was introduced to the market in 1998, and is now available as combination therapy.

Hepatitis B

Interferon-alfa, along with lamivudine and adefovir are current first-line therapies for the treatment of chronic HBV.[6, 7] Recommendations from the American Association for the Study of Liver Diseases for the treatment of chronic HBV infection are described in Table 2.

Table 2. Recommendations from the American Association for the Study of Liver Diseases for the Treatment of Chronic Hepatitis B Infection[6, 7*]

Presence of HbeAg	Presence of HBV DNA†	ALT Level	Recommended Treatment
Yes	Yes	=2 x ULN	Observation only. Consider treatment when ALT becomes elevated.
Yes	Yes	>2 x ULN	• IFN-a for 16 weeks *OR* • Lamivudine for minimum of 1 year, continue 3-6 months after HBeAg seroconversion *OR* • Adefovir for minimum of 1 year • If nonresponder with IFN-a or contraindication, use lamivudine or adefovir • Adefovir in patients with lamivudine resistance.
No	Yes	>2 x ULN	IFN-a, lamivudine, or adefovir can be used; however, IFN-a or adefovir is preferred due to need for long-term therapy. • IFN-a for 16 weeks *OR* • Adefovir for minimum of 1 year *OR* • Lamivudine for minimum of 1 year, continue 3-6 months after HBeAg seroconversion • If nonresponder with IFN-a or contraindication, use lamivudine or adefovir • Adefovir in patients with lamivudine resistance.
No	No	= x ULN	Observation only.
Yes or No	Yes	Cirrhosis	• Compensated cirrhosis: lamivudine or adefovir • Decompensated cirrhosis: lamivudine or adefovir; refer for liver transplant; IFN-a is contraindicated.
Yes or No	No	Cirrhosis	• Compensated: observation only. • Decompensated: refer for liver transplant.

*HBeAg indicates hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; ULN, upper limit of normal; IFN-a, interferon-alfa.
†Presence indicates HBV DNA $>10^5$ copies/mL, which was arbitrarily chosen.

Hepatitis C

For the treatment of hepatitis C, interferon, ribavirin, or a combination of interferon and ribavirin are indicated for the treatment of chronic disease.[8] The American Association for the study of Liver Diseases for the treatment of chronic HCV recommends treatment for HCV in patients 18 years of age and older, based on the genotype. Genotype-specific treatment recommendations include:

Genotype-1 HCV Infection

- Peginterferon plus ribavirin for 48 weeks.
- Ribavirin dose = 1000mg for patients =75kg and 1,200mg for patients >75kg.

Genotype-2 or Genotype-3 HCV Infection

- Peginterferon plus ribavirin for 24 weeks
- Ribavirin dose = 800mg

Genotypes 4, 5, and 6 HCV Infection

- Insufficient data to provide recommendations

III. Comparative Indications of the Interferons

Most of the interferons are indicated for use in their specific indications for patients age 18 and older. Treatment can be initiated with a liver biopsy and a serum test for the presence of antibody to HCV are performed to establish the diagnosis. Other causes of hepatitis, including hepatitis B, should be considered, as well as history of blood or blood-product exposure. Treatment with interferons for hepatitis C is also dependent on the patient having compensated liver disease. The following constitutes compensated liver disease:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation.
- Bilirubin (= 2mg/dl)
- Albumin (stable and within normal limits)
- Prothrombin time (<3 seconds prolonged)
- WBC (=3000/mm^3)
- Platelets (=70,000/mm^3)

Table 3 compares the indications for the interferons.

Table 3. FDA-Approved Indications for the Interferons[2, 3, 9, 10]

Drug	Chronic Hepatitis C	Hairy Cell Leukemia	AIDS-related Kaposi's sarcoma	Chronic myelogenous leukemia (CML)	Chronic Hepatitis B	Condylomata acuminata	Follicular lymphoma	Malignant Melanoma
Interferon alfa -2a, recomb. (Roferon-A)	v	v	v‡	v†				
Peginterferon alfa-2a (Pegasys)	v8							
Peginterferon alfa-2b (PEG-Intron)	v*							
Interferon alfa-2b, recomb (Intron A)	v	v	v		v	v	v (Non-Hodgkins)	v
Interferon alfacon-1 (Infergen)	v							
Interferon alfa-N3 (Alferon N)						v (Not for use in patients <18 years)		

*Alone or in combination with ribavirin (Rebetol) in patients with compensated liver disease who have not been previously tested with interferon alpha and are at least 18 years of age.
†Philadelphia chromosome positive CML
‡Use based on likelihood of response, based on clinical manifestations of HIV infection, including prior opportunistic infections.
8Alone or in combination with ribavirin (Copagus)

IV. Pharmacokinetic Parameters of the Interferons

The mechanism by which interferons exert antitumor or antiviral activity is not clearly understood. However, direct antiproliferative action against tumor cells and modulation of the host immune response may play important roles.[2, 3,] Pharmacokinetic data is unavailable or limited for many of the interferons, likely due to little research in this area.

Table 4 illustrates the pharmacokinetics of the interferons.

Table 4. Pharmacokinetic Parameters of the Interferons[2, 3, 9, 10]

Drug	Bioavailability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Interferon alfa -2a, recomb. (Roferon-A)	Mean: 2020pg/ml (Range: 1500 to 2580pg/ml).	-	-	-	Primarily filtered by the kidney	Mean terminal ½ life: 5.1 hours (Range: 3.7 to 8.5 hours)
Peginterferon alfa-2a (Pegasys)	Mean trough: 16ng/ml (Range: 0 to 15).	-	-	-	-	Mean terminal ½ life: 40 hours (Range: 50 to 140 hours)
Peginterferon alfa-2b (PEG-Intron)†	Mean absorption half-life is 4.6 hours; max. conc. occur between 15 and 44 hours post dose and are sustained for 48-72 hours. There is an increase in bioavailability after multiple doses.	-	-	-	30% renal	Mean elimination ½ life: 40 hours
Interferon alfa-2b, recomb (Intron A)**	Serum concentrations of IM and SQ doses are similar; peak concentrations 30 min after infusion.			Kidney may be the main site of catabolism		2-3 hours
Interferon alfacon-1 (Infergen)*	Levels after SQ injection of 1, 3, or 9mcg were too low to be detected by ELISA or by inhibition of viral effect; a dose response relationship has been observed.	-	-	-	-	-
Interferon alfa-N3 (Alferon N)	Plasma concentrations of interferon when used intralesionally were below the detection (e.g. = 3IU/ml).	-	-	-	-	-

* Data from normal, healthy volunteers, not patients with hepatitis C.
**No pharmacokinetic data is available on intra-lesional use.
†Pegylation of interferon alfa 2-b produces a product (PEG-Intron) whose clearance is lower than that of nonpegylated interferon alfa-2b. When compared with Intron A, PEG-Intron (1.0mcg/kg) has approximately a 7-fold lower mean apparent clearance and a 5-fold greater mean half-life permitting a reduced dosing frequency. At effective therapeutic doses, PEG-Intron has approximately 10-fold greater Cmax and 50-fold greater AUC than interferon alfa-2b.

V. Drug Interactions

Drug interactions with some of the interferons (Intron A, Roferon-A, Infergen) have not been fully evaluated. Caution should be used with other potentially myelosuppressive agents such as zidovudine. Drug interactions have not been reported with intra-lesional administration of interferons, as little drug circulates systemically. Table 5 lists other known interactions with the interferons.

Table 5. Drug Interactions of the Interferons[9, 2, 11]

Drug	Interaction	Mechanism
Theophylline	Increase in theophylline levels, resulting in a 100% increase in serum theophylline levels.	Mechanism is unknown. Interaction may cause moderate-to-major effects; data are very limited. Patients with pre-existing increased theophylline clearance (smokers) are at risk of this interaction .
Drugs metabolized by the cytochrome P-450 system	Theoretical increases in serum levels may occur with these drugs.	Mechanism is unknown.
Peginterferon alfa-2a (Pegasys)	Peginterferon alfa-2a and ribavirin	Peginterferon alfa-2a and ribavirin has been shown in vitro to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased anti-retroviral activity.
Peginterferon alfa-2a (Pegasys)	Peginterferon alfa-2a and didanosine	Exposure to didanosine or its active metabolite is increased when didanosine is co-administered with ribavirin.
Alpha Interferons	Alpha interferons and eflornithine	Systemic eflornithine in combination with alpha interferons has resulted in hearing loss at multiple frequencies in selected patients. However, hearing loss has been associated with the use of systemic eflornithine alone. Hearing loss may be more pronounced in patients that already have a hearing impairment. The health care provider might consider serial audiograms if eflornithine is used alone or in combination with alpha interferons.

VI. Adverse Drug Events of the Interferons

Black Box Warning
A black box warning is associated with the interferons in this class (except for Alferon-A).[2, 9] Additional black box warnings are associated with ribavirin (see interferon combination pharmacotherapy review) use and pregnancy.

> Alpha interferons, including interferon alfa-2a, recombinant, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Closely monitor patients with periodic clinical and laboratory evaluations. Withdraw patients with persistently severe or worsening signs or symptoms of these conditions from therapy. In many, but not all cases, these disorders resolve after stopping interferon alfa-2a, recombinant therapy.

Adverse events with intralesional administration of interferons (and Alferon N) include flu-like symptoms, consisting of fever, myalgias, and /or headache. These episodes were reported primarily after the first treatment session in 30% of patients. With Alferon N, these adverse events abated with repeated dosing so that incidences were similar after 3-4 weeks of treatment. Flu-like symptoms are also common with systemic administration of interferons. Another common adverse event is thinning of the hair. Table 6 lists adverse events for the single entity interferons.

Table 6. Common Adverse Events (%) Reported for the Interferons[2, 3, 9, 10]

Adverse Event	Interferon alfa 2a, recomb	Peginterferon alfa 2a,	Peginterferon alfa-2b	Interferon alfa-2b, recomb	Interferon alfacon-1	Interferon alfa-n3
Body as a Whole						
Malaise			7	3-19	11	9
Cardiovascular						
Edema						
Hypotension	11				9	
Hypertension	11				3	
Digestive System						
Abdominal Pain						
Nausea	12	15	15	17-66	40	4
Vomiting	39	23	26	2-32	12	3
Diarrhea	34	16	7	2-45	29	
Epigastric distress	14	17	18			
Appetite decrease		17	20	1-69	24	
Central Nervous System						
Dizziness						
Fatigue	13	16	12		22	9
Fever	58	50	52		69	14
Headache	28	54	22		61	40
Meningeal Signs	52		56		82	31
Raised Intracranial Pressure						
Collapse						
Confusion						
Drowsiness	7				4	
Hepatic						
Abnormal LFTs (incr.)						
Hepatitis						
Hepatic failure						
Skin and Appendages						
Alopecia	19	23	22	8-38	14	
Rash	8	5	6	1-25	13	
Pruritus	7	12	12	1-11	13	
Hematologic						
Neutropenia						
Agranulocytosis						
Renal						
Abnormal kidney fxn						
Acute kidney failure						

VII. Dosing and Administration for the Interferons

Table 7. Dosing and Administration for the Interferons[2, 3, 9, 10]

Drug	Availability	Dose /Frequency/Duration
Interferon Alfa-2a, Recombinant (Roferon-A)	3 million IU/syringe, 6 million IU/syringe, 9 million IU/syringe	• **Chronic hepatitis**: 3 million IU 3 times per week given IM or SC for 48 to 52 weeks. Alternative therapy: 6 million IU 3 times/week for the first 12 weeks, then 3 million IU 3times/week for 36 weeks. • **Hairy cell leukemia induction dose**: 3 million IU given IM or SC daily for 16 to 24 weeks. Maintenance dose: 3 million IU given IM or SC three times/week. • **AIDS-related Kaposi's sarcoma induction dose**: 36 million IU daily for 10 to 12 weeks, given IM or SC. Maintenance dose: 36 million IU 3 times/week. An escalating schedule of 3, 9, and 18 million IU daily for 3 days followed by 36 million IU daily for the remainder of the 10-to 12-week induction period also has produced equivalent therapeutic benefit with some amelioration of the acute toxicity in some patients. • **CML induction dose**: 9 million IU daily given IM or SC. Short-term tolerance may be improved by gradually increasing the dose of interferon alfa-2a over the first week of administration from 3 million IU daily for 3 days to 6 million IU daily for 3 days to the target dose of 9 million IU daily for the duration of the treatment period. Maintenance: Optimal dose and duration of therapy have not been determined.
Peginterferon alfa-2a (Pegasys)	180 mcg vial	The recommended dose of peginterferon alfa-2a is 180mcg (1.0mL) once weekly for 48 weeks by SC administration in the abdomen or thigh. In patients with end-stage renal disease requiring hemodialysis, dose reduction to 135mcg is recommended. Signs and symptoms of interferon toxicity should be closely monitored. In patients with progressive ALT increases above baseline values, the dose of peginterferon alfa-2a should be reduced to 90mcg. If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued. Peginterferon alfa-2a should be administered with caution in patients with the following conditions: baseline neutrophil counts <1500 cells/mm^3; with baseline platelet counts <90,000 cells/mm^3; baseline hemoglobin <10 g/d; with pre-existing cardiac disease; endocrine disorders or auto-immune disorders; or with depression.
Peginterferon alfa-2b (Peg-Intron)	50mcg/0.5ml, 80mcg/0.5ml, 120mcg/0.5ml, 150mcg/0.5ml	Recommended dosage regimen is 1.0mcg/kg/week for one year. Patients with impairment of renal function should be closely monitored for signs and symptoms of interferon toxicity and doses should be adjusted accordingly. Peginterferon alfa-2b should be used with caution in patients with creatinine clearance <50mL/min. For patients with a history of stable cardiac disease receiving peginterferon alfa-2b in combination with ribavirin, the peginterferon alfa-2b dose should be reduced by half and the ribavirin dose by 200mg/day if a >2g/dL decrease in hemoglobin is observed during any 4 week period.
Interferon alfa-2b, recomb. (Intron-A)	3 million IU/vial, 5M IU/vial 10M IU/vial, 18M IU/vial, 25M IU/vial, 50M IU/vial, 3M, 5M, 10M IU/dose pens	• **Hairy-cell leukemia**: 2 million IU/m^2 IM or SC 3 times/week for up to 6 months. • **Malignant melanoma**: 20 million IU/ m^2 IV infusion on 5 consecutive to 24 weeks. Maintenance dosage is 10 million IU/ m^2 SC 3 times/ week for 48 weeks. • **Follicular lymphoma**: 5 million IU SC 3 times/week for up to 18 months in conjunction with an antracycline-containing chemotherapy regimen. • **Condylomata acuminata**: 1 million IU/lesion 3 times/week for 3 weeks

		on alternate days intralesionally for 4 to 8 weeks. If results are not satisfactory after 12 to 16 weeks, a second course of therapy may be initiated. • **AIDS-related Kaposi's sarcoma**: 30 million IU/ m^2 3 times/week SC or IM. Average dose tolerated at the end of 12 weeks of therapy is 110 million IU/week and 75 million IU/week at end of 24 weeks of therapy. • **Chronic hepatitis C**: 3 million IU 3 times/week SC or IM. In patients tolerating therapy with normalization of ALT at 16 weeks of treatment, extend therapy to 18 to 24 months at 3 million IU 3 times/week to improve the sustained response. Consider discontinuing therapy in if not responsive after 16 weeks. If severe adverse reactions develop, modify the dose (50% reduction) or temporarily discontinue therapy until reactions abate. • **Chronic hepatitis B**: Adults: 30 to 35 million IU/week SC or IM, as 5 million IU daily or 10 million IU 3 times/week for 16 weeks. Pediatrics: 3 million IU/m^2 3 times/week for the first week of therapy followed by dose escalation to 6 million IU/m^2 3 times/week (maximum of 10 million IU 3 times/week) administered SC for a total therapy duration of 16 to 24 weeks.
Interferon alfacon-1 (Infergen)	9mcg and 15mcg single-dose vials	Recommended dose is 9mcg three times/week SC for 24 weeks. There should be at least 48 hours between each dose. Patients who do not respond or who have a relapse after discontinuation may use 15mcg 3 times weekly for up to 48 weeks. Use with caution in patients with a history of depression. Use with caution in patients with cardiac disease.
Interferon alfa-n3 (Alferon-N)	5 million IU vial	Recommended dose is 250,000 IU per wart and is used twice weekly for up to 8 weeks. The maximum recommended dose per treatment session is 2.5 million IU. A minimum effective dose has not been established. The drug should be used with caution in patients with debilitating medical conditions, e.g. diabetes mellitus with ketoacidosis, unstable angina, uncontrolled congestive heart disease, etc.

Special Dosing Considerations

Brand of interferons should not be changed within a single treatment regimen, without medical consultation, due to variances in dosage and adverse events.[9]

Table 8. Special Dosing Considerations for the Interferons[2, 3, 5, 9, 10, 12]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category
Interferon alfa-2a, recomb. (Roferon-A)	Dose-limiting renal toxicities are unusual. No adjustments for renal disease.	Dose-limiting liver toxicities are unusual. Has not been formally studied in decompensated liver disease.	Use in children with Ph-positive adult-type CML supported by evidence from well-controlled studies. Safety and efficacy has not been established for any other indication in patients under 18 years old.	Category C
Peginterferon alfa-2a (Pegasys)	Use caution in patients with a CrCl <50ml/min.	Patients with decompensated hepatic disease should not be treated. In patients with progressive ALT increases above baseline values, the dose of peginterferon alfa-2a should be reduced to 135mcg SC once weekly. If ALT increases are progressive despite dose	Safety and efficacy has not been established in patients under 18 years old.	Category C

		reduction or are accompanied by increased bilirubin or evidence of hepatic decompensation, immediately discontinue therapy.		
Peginterferon alfa-2b (PEG-Intron)	CrCl < 50 ml/min: Specific guidelines for dosage adjustments are not available; the clearance of peginterferon alfa-2b is reduced by about 50% in these patients.	Patients with decompensated hepatic disease (e.g., active alcoholism, ascites, coagulopathy, hypoalbuminemia, or jaundice) should not be treated with peginterferon alfa-2b.	Safety and efficacy has not been established in patients under 18 years old.	Category C
Interferon alfa-2b, recomb. (Intron-A)	Specific guidelines for dosage adjustments in renal impairment are not available.	Interferon alfa-2b has not been studied in patients with decompensated hepatic disease. Patients with decompensated hepatic disease should not be treated with interferon alfa-2b.	Safety and efficacy in children less than 18 years of age have not been established for indications other than chronic hepatitis B (in children 1 year of age and older).	Category C
Interferon alfacon-1 (Infergen)	Specific guidelines for dosage adjustments in renal impairment are not available.	Interferon alfacon-1 has not been studied in patients with decompensated hepatic disease. Patients with decompensated hepatic disease should not be treated with interferon alfacon-1.	Safety and efficacy has not been established in patients under 18 years old.	Category C
Interferon alfa-n3 (Alferon-N)	Specific guidelines for dosage adjustments in renal impairment are not available.	Interferon alfa-n3 has not been studied in patients with decompensated hepatic disease. Patients with decompensated hepatic disease should not be treated with interferon alfa-n3.	Safety and efficacy has not been established in patients under 18 years old.	Category C

VIII. Comparative Effectiveness of the Interferons

Many chronic hepatitis C studies has shown significantly higher results with interferon/ribavirin combination therapy compared to interferon monotherapy.[5] Monotherapy with interferons is generally reserved for patients who cannot tolerate or have a contraindication to ribavirin (pregnancy, breast feeding, hemoglobinopathy, pancreatitis, renal failure, sickle cell disease, and thalassemia).

Table 9. Additional Outcomes Evidence for the Interferons

Study	Sample	Protocol	Results
Hepatitis			
Damen M, et al.[13]	n=8	Interferon alfa-2b or placebo for 24 weeks or up to 156 weeks for non-responders	In assessing the efficacy of interferon alfa-2b in treating chronic hepatitis C, in this multicenter, randomized, controlled trial: • Significantly more patients achieved a sustained virologic response (SVR) after long-term treatment compared with standard treatment. • Among patients that relapsed during or after standard treatment, 78 percent achieved SVR upon long-term treatment. • In patients that failed to respond to standard treatment, no virological response was observed during long-term treatment.
Boucher EJ, et al.[14]	n=187	Interferon-alpha2b or interferon-alpha2b and ribavirin for 12 months	In investigating the long-term efficacy of a 12-month course of interferon with or without ribavirin in chronic hepatitis C relapsers: • Significantly more patients achieved a sustained virological response in the interferon/ribavirin group compared with the interferon group. • A significant histological improvement was observed in both treatment groups. • The Metavir fibrosis scores remained unchanged.
Senturk H, et al.[15]	n=125	Interferon-alpha2b or interferon-alpha 2b and ribavirin for 48 weeks	In comparing the efficacy of interferon-alpha2b induction treatment in combination with ribavirin to interferon-alpha2b induction alone in chronic hepatitis C, in this multi-center, randomized, controlled trial: • No significant differences were found in regards to response rate between groups. • Significantly more patients in the interferon group relapsed (54%) compared with the interferon/ribavirin group (26%; P=0.002); resulting in significantly higher sustained virologic response rate for the interferon/ribavirin group.
Verbaan HP, et al.[16]	n=116	Interferon alfa-2b or interferon alfa-2b and ribavirin for 52 weeks	In evaluating the efficacy and safety of therapy for patients with histologically mild hepatitis C liver disease, in this randomized, double-blind, placebo-controlled trial: • Significantly more patients on combination therapy experienced a sustained virological response (SVR) compared with patients receiving interferon alone. • Sustained response rate was higher with combination therapy than monotherapy both in genotype non-1 and in genotype 1.
Malik AH, et al.[17]	n=25	Interferon alfa-2b or interferon alfa-2b and ribavirin for 36 weeks	In comparing the efficacy and safety of re-treatment with an induction regimen of high-dose interferon alfa-2b, with or without ribavirin, in chronic hepatitis C patients who have not responded to standard dose interferon monotherapy: • Significantly more patients receiving both interferon/ribavirin experienced virological response at the end of treatment compared with patients receiving interferon alone.
Cheng PN, et al.[18]	n=52	Interferon-alpha2b or interferon-alpha2b and ribavirin for 24 weeks	In comparing, in a randomized, double-blind, placebo-controlled study, high-dose interferon-alpha2b with or without ribavirin in the treatment of interferon-relapsed chronic hepatitis C: • No detectable HCV RNA levels were observed in 92 percent of interferon/ribavirin patients and 81 percent of interferon patients. • Significantly higher sustained virological response rate was seen in patients treated with interferon and ribavirin than those treated with interferon (69% vs 23%, p<0.001). • Patients with either initially high levels of viral concentration or with genotype 1 responded poorly.
Chapman BA, et al.[19]	n=32	Interferon for 48 weeks or interferon	In comparing the efficacy of a descalating dose of interferon for 48 weeks versus a combination therapy of interferon and ribavirin for 24 weeks for the

		and ribavirin for 24 weeks	treatment of hepatitis C in patients who relapsed within 6 months of cessation of standard interferon therapy: • The sustained virological response (HCV RNA negative) was 50 percent for both groups. • The biochemical response (transaminase normalization) correlated with the virological response.
Hoofnagle JH, et al.[20]	n=34	Ribavirin or placebo	In assessing the efficacy and safety of maintenance therapy with ribavirin in patients with chronic hepatitis C who failed to respond to combination therapy with interferon alfa and ribavirin: • No overall improvement in symptoms, serum alanine aminotransferase levels, HCV RNA levels, or hepatic histology were seen in patients receiving placebo. • In the ribavirin group, serum alanine aminotransferase levels and necroinflammatory features of liver histology were improved, whereas symptoms, HCV RNA levels, and hepatic fibrosis scores were not changed significantly from baseline.
Pockros PJ, et al.[21]	n=639	Peginterferon alpha-2a 135microg/wk, peginterferon alpha-2a 180microg/wk and interferon alpha-2a in patients with chronic hepatitis C, for 48 weeks	In evaluating the efficacy and safety of two-dose regiment of peginterferon alpha-2a versus interferon alpha-2a: • Sustained virological responses were significantly higher with peginterferon alpha-2a than with interferon alpha-2a 3 MIU (28% in the 135microg and 180 microg peginterferon alpha-2a groups vs 11% with interferon alpha-2a, p = 0.001). • The proportion of patients with clinically significant histological improvement was lower in the peginterferon alpha-2a 135 microg (48%) than the 180 microg group (58%, p = 0.035 vs peginterferon alpha-2a 135 microg), but similar to that in the interferon alpha-2a group (45%, p = 0.820 vs peginterferon alpha-2a 135 microg and p = 0.017 vs peginterferon alpha-2a 180 microg, respectively). • The overall safety profiles were similar for the three treatments. • Summary: In patients with chronic hepatitis C, peginterferon alpha-2a 135 microg/wk and 180 microg/wk produced similar sustained virological response rates, both of which were significantly higher than that achieved with interferon alpha-2a thrice weekly. A significantly higher proportion of patients treated with the 180 microg dose of peginterferon alpha-2a had clinically significant histological improvement.
Lindsay KL, et al.[22]	N=1219	Peginterferon alfa-2b (Peg-Intron) at a dose of 3MIU three times weekly vs. interferon alfa-2b at a dose of 0.5, 1, or 1.5mcg/kg, for 48 weeks	In evaluating the comparative efficacy of peginterferon alfa-2b with interferon alfa-2b as initial therapy for chronic hepatitis C: • All three peginterferon alfa-2b doses significantly (p=0.042) improved virologic response rates after treatment and after follow-up (an additional 24 weeks), as compared to interferon alfa-2b. • All three peginterferon alfa-2b doses decreased liver inflammation to a greater extent than did interferon alfa-2b. • No new adverse events were reported, and the majority of adverse events and changes in laboratory values were mild or moderate. • Summary: Peginterferon alfa-2b maintained or surpassed the clinical efficacy of interferon alfa-2b while preserving its safety profile.
Condylomata Acuminata			
Douglas JM, et al.[23]	n=97	Interferon alpha 2a + podophyllin vs. podophyllin alone	To determine the value of combining interferon with standard local therapy in the treatment of human papillomavirus: • Interferon alpha 2b (1.5 x 10(6) IU) was injected intralesionally and podophyllin resin applied topically to each of three warts once weekly for 3 weeks. • Maximal responses occurred within 2 weeks of therapy, and overall there was complete clearance of treated warts in 67% of interferon and podophyllin versus 42% of podophyllin recipients (P less than 0.05, chi 2). • Clearance rates were greater in women, patients with warts of less than or equal to 12 months' duration, and HIV-seronegative patients. • Summary: Treatment courses of anogenital warts with intralesional interferon, enhanced the effect of topical podophyllin.
Boot JM, et al. [24]	n=11	Interferon alfa-2b	In evaluating the safety and efficacy of intralesionally administered interferon

			alfa-2b in patients with condylomata acuminate, in whom application of podophyllum resin was unsuccessful: • Three warts from each patient were injected with 10(6) IU interferon alfa-2b three times a week for three weeks. Treatment was followed by a 13 week observation period. • Interferon alfa-2b treatment resulted in a highly significant (p less than 0.0001) reduction in the mean size of the treated warts, which decreased from an initial size of 29 mm2 to 2-3 mm2 by week 16. • In six out of the 10 patients completing the trial, both the test condylomata and adjacent control warts cleared completely; a recurrence was observed in one of these six patients. • Influenza like symptoms (headache and myalgia) were the most common side effects reported, though they were mild in nature and not disabling.
Welander CE, et al.[25]	n=42	Interferon alafa-2b	This double-blind, placebo-controlled study looked at which intralesional interferon alfe-2b was evaluated in the treatment of genital warts: • There were 43.8% of patients on the interferon treatment arm of the double-blind portion of the study who had complete disappearance of all warts, with an additional 25% of patients showing greater than 50% shrinkage of visible warts. • On the placebo arm 14.3% showed a complete response, with an additional 14.3% showing greater than 50% shrinkage. • This difference between interferon and placebo treatment was statistically significant (p less than 0.03). • Summary: The authors concluded that intralesional interferon alfa-2b has significant activity in the treatment of genital warts.
Hairy Cell Leukemia			
Rai KR, et al.[26]	n=55	Recombinant alpha interferon-2b given three times weekly for 1 year	In evaluating the role of interferon alpha in therapy of previously untreated active hairy cell leukemia: • Treatment was well tolerated; toxicity mainly consisted of flu-like syndrome and pancytopenia, both of a transient nature. • Seventy-three percent of patients had objective beneficial responses with 8.3 months median time to achieve at least a partial response (PR). • After 1 year of therapy, there was a continual trend towards relapse, but 28% remained in remission beyond 6 years. • Forty-six patients (83%) are alive at 6 years. • Among the 40 patients who achieved at least a partial response, there were 28 with splenomegaly at the beginning of study: the spleen size was reduced in all with interferon alpha therapy and none required splenectomy. • Summary: This study confirms the results of other investigators, and demonstrates that recombinant alpha interferon-2b is an effective agent for treatment of hairy cell leukemia.
Federico M, et al.[27]	n=177	Interferon alpha	To confirm the efficacy of alpha interferon as a first-line treatment for hairy cell leukemia: • Treatment of HCL patients with alpha-IFN at the onset of the disease resulted in 28 complete remissions, 103 partial responses (62.0%), and 27 minor remissions (16.3%). • Patients treated with different alpha-IFNs achieved similar results: the overall response rate (CR + PR + MR) was 92.7%, 97.2%, and 95.3% for patients treated with r-alpha-2a, r-alpha 2b, and alpha-N1, respectively. • The presence of a leukemic phase and a poor performance status were associated with a statistically significant lower response rate. • Patients who were randomly assigned and underwent splenectomy after achieving a PR had a better but not significant 4-year progression-free survival than cases randomized for observation (53% vs. 22%, p = 0.116). • Overall, 5 patients died after study entry, with an actuarial 5-year survival rate of 96% for the entire group of 166 patients. • Summary: Initial therapy with alpha-IFN, regardless of the type of

			alpha-IFN used, induces satisfactory responses in the majority of patients with HCL, but in most instances discontinuation of treatment results in recurrence of disease. In most cases alpha-IFN improves the performance status of patients and favors a satisfactory bone marrow recovery and thus could still play a role in the initial management of the disease. Although splenectomy following alpha-IFN could prolong the progression free survival, its use should be restricted to selected cases.
Kaposi Sarcoma			
Opravil M, et al.[28]	n=26	Interferon-alpha 2a + zidovudine vs. bleomycin + zidovudine	In evaluating the efficacy and toxicity of interferon –alpha 2a and bleomycin, each combined with zidovudine in the treatment of Kaposi's sarcoma: • Complete or partial response was achieved in one (8%) of 12 evaluable patients on interferon and in 2 (20%) of 10 patients on bleomycin (P = 0.43) during 4.7 and 5.3 months of treatment, respectively. • The tolerability was comparable. During extended follow up, survival time was 24 and 13 months in the interferon and bleomycin arm, respectively. • In a multivariate Cox regression analysis, CD4 lymphocytes <200/microl (relative risk 3.74; 95% CI: 1.30-10.8) and randomization to interferon (relative risk 0.37; 95% CI: 0.15-0.90) were significantly predictive of mortality. • New AIDS-related events occurred more frequently in patients who had received bleomycin. • The antiviral activity of interferon-alpha or the chemotherapy-mediated increase in the risk for opportunistic infections may explain these differences.
Krown SE, et al.[29]	n=68	Low dose and intermediate dose interferon-alpha 2b with didanosine in patients with AIDS related Kaposi's sarcoma	In studying the efficacy and safety of a low and intermediate dose of interferon-alpha 2b with didanosine: • The response rate was 40% in the low-dose group (95% CI, 24-58) and 55% in the intermediate-dose group (95% CI, 36-72) (p = 0.338). • The median response duration was approximately 110 weeks in both groups. • Intermediate-dose IFN induced grade 3/4 neutropenia more often (21% vs. 3%, p = 0.048) and grade 3/4 toxicity faster (p = 0.0231) and necessitated treatment discontinuation earlier for drug-related toxicities (p = 0.0416) than low-dose IFN. • There were no significant differences in survival between the treatment groups. • Baseline CD4 count was the only significant factor predicting response. • Once-daily low-dose and intermediate-dose IFN-alpha2b induced similar response rates, which were achieved without optimal antiretroviral therapy. • Summary: The slightly higher response rate in the intermediate-dose group was offset by its significantly poorer tolerance. These findings justify the use of lower, well-tolerated IFN doses for treatment of KS with currently used antiretroviral regimens.

Additional Evidence

Dose Simplification: Several studies were found comparing the efficacy and safety of daily interferon alfa therapy with thrice weekly interferon alfa therapy with or without ribavirin. Multiple studies have found no difference in combination therapy with daily induction treatment compared with combination therapy with thrice weekly dosing.[30, 31, 32] However, one study found that combination therapy is more effective when interferon alfa is administered daily for the first 24 weeks in naïve patients with chronic hepatitis C.[33] Other studies have tried to achieve dose simplification in looking at the duration of therapy. Numerous studies have addressed the efficacy of combination therapy over 24 weeks or 48 weeks. Multiple studies have found that combination therapy with interferon and ribavirin for 48 weeks was more effective than combination therapy for 24 weeks.[34, 35, 36]

Additionally, a study by Kaito et al. that looked at the efficacy of twice-a-day (group A) versus once-a-day (group B) interferon-beta for chronic hepatitis C.[37] The rate of sustained virological response was significantly higher in group A (14 of 22 patients, 63.6%) than in group B (6 of 20 patients, 30.0%) ($p < 0.05$). Among patients with hepatitis C virus-RNA level less than 1 Meq/mL, the sustained virological response rate was significantly higher in group A (13 of 15 patients, 86.7%) than in group B (5 of 12 patients, 41.7%) ($p < 0.05$). In this study, twice-a-day interferon-beta therapy was more effective than once-a-day interferon-beta for the treatment of chronic hepatitis C patients with hepatitis C virus-RNA levels less than 1 Meq/mL.

Stable Therapy: No studies were found utilizing a literature search of Medline regarding changing therapies once stabilized on interferon or peginterferon therapy. However, it is recommended that the specific preparation selected for the patient be used throughout the treatment regimen. This is due to differences in potencies and differences in recommended dosages and routes of administration among the various commercially available interferon alfa and peginterferon alfa preparations.[38]

Impact on Physician Visits: A literature search of Medline did not reveal clinical literature relevant to use of the interferons and their impact on physician visits.

IX. Conclusions

Use of interferons has evolved in the past ten years. Use of these agents is for unique diseases, with the interferons having a wide range of indications. Specifically, the pegylated interferons have been shown to offer superior clinical efficacy compared to the non-pegylated interferons, for the treatment of hepatitis C. Additionally, clinical treatment guidelines for hepatitis stress the importance of combination therapy with ribavirin. Interferon monotherapy for hepatitis is generally reserved for patients who cannot tolerate or have a contraindication to ribavirin. The indicated interferons for condylomata acuminate, hairy cell leukemia, and Kaposi's sarcoma have shown promise for these conditions, although one interferon hasn't been shown to be more effective. One clinical study suggested interferon use for condylomata acuminata is effective when used after other therapies have failed.

When comparing agents within the interferons class, the pegylated interferons (PEG-Intron and Pegasys) offer significant clinical advantage when used for hepatitis C. However, at this time, there is not a role for these agents in general use. Due to the narrow indication with limited usage, these interferons should be available for special needs/circumstances that require medical justification through the prior authorization process. After clinical circumstances are explored, proper medical justification will provide patient access to these agents.

The remaining agents in this class are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand interferon is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacotherapy Review of the Nucleoside / Nucleotide Agents
Combination Agents
AHFS 081832
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I. Overview

As previously mentioned in the evidence based treatment guidelines, combination interferon with ribavirin is the standard treatment for hepatitis C. Oral ribavirin is available in a single entity dose formulation (Rebetol or Copegus) or is packaged together with interferon alfa-2b (Intron A). The single entity oral ribavirin can be used together with a single entity interferon. The single entity ribavirin component has been reviewed in a separate pharmacotherapy review (Nucleosides and Nucleotides). This review encompasses all dosage forms and strengths of the combination interferon alfa-2b and ribavirin. No generic formulations are available for the drugs in this class.

Table 1. Combination Nucleosides / Nucleotides in this Review

Generic Name	Formulation	Example Brand Name
Interferon alfa-2b / ribavirin	Injection/oral combination product	Rebetron

No generic formulations are available.

II. Indications of the Combination Nucleosides / Nucleotides

Table 2. Indications of the Combination Nucleosides / Nucleotides

Drug	Indication
Interferon alfa-2b / ribavirin (Rebetron)	Treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy. Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication.

III. Pharmacokinetics of the Combination Nucleosides / Nucleotides

The mechanism of action of inhibition of hepatitis C virus RNA by combination therapy with ribavirin and interferon alfa-2b has not been established.

Table 3. Pharmacokinetic Parameters of the Combination Nucleosides / Nucleotides When Administered to Patients With Hepatitis C[9]

Parameter	Single Dose Interferon alfa-2b/ ribavirin 3MIU	Multiple Dose Interferon alfa-2b/ ribavirin 3MIU TIW	Single Dose Ribavirin 600mg	Multiple Dose Ribavirin 600mg BID
Tmax (hr)	7 (44)	5 (37)	1.7 (46)***	3 (60)
Cmax*	13.9 (32)	29.7 (33)	782 (37)	3680 (85)
AUC_{tf}**	142 (43)	333 (39)	13400 (48)	22800 (25)
T1/2 (hr)	6.8 (24)	6.5 (29)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	-	-	2825 (9)†	-
Apparent Clearance (L/hr)	14.3 (17)	-	38.2 (40)	-
Absolute Bioavailability	-	-	64% (44)††	-

*IU/ml for interferon alfa-2b and ng/ml for ribavirin.
**IU.hr/ml for interferon alfa-2b and ng.hr/ml for ribavirin.
***n=11
†Data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; n=5.
††n=6

IV. Drug Interactions of the Combination Nucleosides / Nucleotides

Table 4. Drug Interactions of the Combination Nucleosides / Nucleotides [9, 11]

Drug	Significance	Interaction	Mechanism
Theophylline, aminophylline, oxtriphylline	Interaction may cause moderate-to-major effects; data are very limited.	Increases the effect of theophylline.	Mechanism is unknown.
Warfarin	Interaction may cause moderate-to-major effects; data are very limited.	Decreases the anticoagulant effect of warfarin.	Mechanism is unknown.
Mephalan	Interaction may cause minor-to-major effects; occurrence is unlikely or there is no good evidence of an altered clinical effect.	Decreased serum mephalan concentration.	Increased elimination of melphalan due to interferon-induced fever.

V. Adverse Events of the Combination Nucleosides / Nucleotides

The primary toxicity of ribavirin is hemolytic anemia. The most common adverse events associated with the interferon component was headache, fatigue, nausea, myalgia, insomnia, depression and alopecia.[2, 3, 9] Other adverse events are similar to those listed for the single entity components. The following black box warning applies to interferon alfa and ribavirin. Table 5 describes adverse events in previously treated patients.

Black Box Warning

Alpha interferons:
Alpha interferons, including peginterferon alfa-2a, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Closely monitor patients with periodic clinical and laboratory evaluations. Withdraw therapy in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a treatment.

Use with ribavirin:
Ribavirin may cause birth defects and/or death of the fetus. Take extreme care to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic; consider it a potential carcinogen.

Table 5. Selected Treatment-Emergent Adverse Events: Previously Untreated Patients[9] 24 weeks of Treatment

Adverse Event	Intron A plus Rebetol n=228	Intron A plus Placebo n=231
Application Site Disorders		
Injection site inflammation	13	10
Injection site reaction	7	9
Body as a Whole		
Headache	63	63
Fatigue	68	62
Rigors	40	32
Fever	37	35
Influenza-like symptoms	14	18
Asthenia	9	4
Chest Pain	5	4
Central and Peripheral Nervous System Disorders		
Dizziness	17	15
Gastrointestinal System		
Nausea	38	35
Anorexia	27	16
Vomiting	14	6
Dyspepsia	11	10
Musculoskeletal System		
Myalgia	61	57
Arthralgia	30	27
Musculoskeletal pain	20	26
Psychiatric Disorders		
Insomnia	39	27
Irritability	23	19
Depression	32	25
Emotional lability	7	6
Concentration impaired	11	14
Nervousness	4	2
Respiratory System Disorders		
Dyspnea	19	9
Sinusitis	9	7
Skin and Appendages		
Alopecia	28	27
Rash	20	9
Pruritus	21	9
Special Senses, Other		
Taste perversion	7	4

Laboratory values[9]

- Hemoglobin: Hemoglobin decreases among patients receiving ribavirin (Rebetol) therapy at week 1, with stabilization by week 4. In patients previously untreated, treated with therapy for 48 weeks, the mean maximum decrease from baseline was 3.1g/dl in a US study and 2.9g/dl in an international study. Hemoglobin levels return to pre-treatment levels within 4-8 weeks of cessation of therapy in most patients. Reduction in hemoglobin levels occurs in two thirds of patients. Dose modification may be required.
- Bilirubin and Uric Acid: Increased in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate and reversed within 4 weeks after treatment discontinuation. This has most commonly been associated with a previous diagnosis of Gilbert's syndrome, but has not been associated with hepatic dysfunction or clinical morbidity.

VI. Dosage and Administration of the Combination Nucleosides / Nucleotides

Table 6. Dosing and Administration of the Combination Nucleosides / Nucleotides

Drug	Availability	Dose /Frequency/Duration
Interferon alfa-2b, recombinant and ribavirin (Rebetron)	Injection/Capsules (combination packages): 3 million IU interferon alfa-2b, recombinant / 0.5mL and 200mg ribavirin	The recommended ribavirin dose depends on the patient's body weight. Body weight = 75 kg ribavirin 400mg (or 600mg) PO each morning plus interferon alfa-2b 3 million IU 3 times/week SC. For patients >75kg, 600mg ribavirin PO each morning plus interferon alfa-2b 3 million IU 3 times/week SC. Therapy should continue for six months.

This combination product comes in the following packages:

Patients = 75 kg : *Intron A* (injection): In single-dose vials (6s), one 18 million IU multidose vial, or one 18 million IU multidose pen. *Rebetol* (capsules): (REBETOL 200mg). White. In 70s.
Patients > 75 kg : *Intron A* (injection): In single-dose vials (6s), one 18 million IU multidose vial, or one 18 million IU multidose pen. *Rebetol* (capsules): (REBETOL 200mg). White. In 84s.
Dose reduction : *Intron A* (injection): In single-dose vials (6s), one 18 million IU multidose vial, or one 18 million IU multidose pen. *Rebetol* (capsules): (REBETOL 200mg). White. In 42s.

Special Dosing Considerations

Table 7. Special Dosing Considerations for the Combination Nucleosides / Nucleotides [2,3,9]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category
Interferon alfa-2b / ribavirin (Rebetron)	CrCl < 50 ml/min: Oral ribavirin therapy is not recommended. Interferon alfa elimination is not affected by changes in renal function.	Patients with severe hepatic dysfunction (Child-Pugh Classification C) have increased Cmax of ribavirin but no changes were noted in AUC values. Interferon does not undergo appreciable hepatic metabolism and, therefore, is not affected by changes in liver function.	When given in combination with interferon alfa, ribavirin capsules are FDA-approved for children >= 5 years of age and ribavirin oral solution is approved for children >= 3 years of age. Suicidal ideation or attempts occurred more frequently among pediatric patients (primarily adolescents), compared to adult patients during treatment and off therapy follow-up. The benefits and risks of treatments should be weighed in children.	Ribavirin-X Interferon alfa-2b-C

VII. Comparative Efficacy of the Combination Nucleosides / Nucleotides

Table 8. Outcomes Evidence for the Combination Nucleosides / Nucleotides

Study	Sample	Treatment / Duration	Results
Torriani FJ, et al.[39]	n=868	Peginterferon alfa-2a plus either ribavirin or placebo, or interferon alfa-2a plus ribavirin for 48 weeks	In comparing the efficacy and safety of three treatment regimens for the treatment of chronic HCV infection in patients who were also infected with HIV: • Overall rate of sustained virologic response (SVR) was significantly higher among the recipients of peginterferon/ribavirin than among those assigned to interferon/ribavirin or peginterferon alone. • Among patients infected with HCV genotype 1, rates of SVR were 29 percent with peginterferon/ribavirin, 14 percent with peginterferon, and 7 percent with interferon/ribavirin. • The corresponding rates among patients infected with HCV genotype 2 or 3 were 62 percent, 36 percent, and 20 percent.
Chung RT, et al.[40]	n=66	Peginterferon alfa-2a plus ribavirin or interferon alfa-2a plus ribavirin for 48 weeks	In comparing two treatment regimens for the treatment of chronic hepatitis C in person coinfected with HIV, in this multi-center, randomized trial: • Treatment with peginterferon/ribavirin was associated with a significantly higher rate of sustained virologic response (SVR) than was treatment with interferon/ribavirin. • In patients treated with peginterferon/ribavirin, significantly more patients with HCV genotype non-1 experienced SVR compared with patients with HCV genotype 1.
Bosques-Padilla F, et al.[41]	n=32	Peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, and peginterferon alfa-2a for 48 weeks	In comparing the efficacy and safety of three treatment regimens in the initial treatment of chronic hepatitis C: • More p atients who received peginterferon alfa-2a plus ribavirin had a sustained virologic response than patients who received interferon alfa-2b plus ribavirin or peginterferon alfa-2a alone. • The overall safety profiles of the three treatments regimens were similar.
Fried MW, et al.[42]	n=1121	Peginterferon alfa-2a plus ribavirin, interferon alfa-2b plus ribavirin, or peginterferon alfa-2a for 48 weeks	In comparing the efficacy and safety of three drug regimens in the initial treatment of chronic hepatitis C: • Significantly higher proportion of patients who received peginterferon/ribavirin had a sustained virologic response than of patients who received interferon/ribavirin or peginterferon alone. • The proportions of patients with HCV genotype 1 who had sustained virologic responses were 46 percent peginterferon/ribavirin, 36 percent interferon/ribavirin, and 21 percent peginterferon alone. • Patients with HCV genotype 1 and high base-line levels of HCV RNA, the proportions of those with sustained virologic responses were 41 percent peginterferon/ribavirin, 33 percent interferon/ribavirin, and 13 percent peginterferon.
Shiffman ML, et al.[43]	n=604	Peginterferon alfa-2a and ribavirin for 48 weeks	In evaluating the efficacy of peginterferon and ribavirin in patients who were nonresponders to previous interferon-based therapy: • 35 percent of patients had no detectable HCV RNA in serum at treatment week 20. • 18% achieved sustained virologic response (SVR). • Reducing the dose of ribavirin from greater than or equal to 80 percent to less than or equal to 60 percent of the starting dose during the first 20 weeks of treatment was associated with a decline in SVR significantly from 21 percent to 11 percent. • Reducing the dose of peginterferon or reducing ribavirin after week 20, when HCV RNA was already undetectable, did not significantly affect SVR.
Hadziyannis SJ, et al.[44]	n=1311	Peginterferon alfa-2a and ribavirin	In assessing the efficacy and safety of 24 or 48 weeks of treatment for chronic hepatitis C: • 48 weeks of treatment was statistically superior to 24 weeks and standard-dose ribavirin was statistically superior to low-dose ribavirin. • Sustained virologic response rates for peginterferon alfa-2a and

			standard-dose ribavirin for 48 weeks were 63 percent overall and 52% in patients with HCV genotype 1.
Barbaro G, et al.[45]	n=423	Interferon alfa-n3 plus ribavirin or interferon alfa-2b plus ribavirin for 24 weeks	In comparing the efficacy and safety of two interferon preparation with ribavirin in treatment-naïve patients with chronic hepatitis C: • No significant differences were found in rates of sustained virologic response between groups. • Total number of adverse events was lower in the interferon alfa-n3 group. • Significantly more patients in the interferon alfa-2b group discontinued therapy due to adverse events.
Younossi, J, et al.[46]	n=118	Interferon alpha-2b and ribavirin or interferon alpha-2b and amantadine for 24 weeks	In comparing the efficacy of two regimens for treatment of hepatitis C non-responders to previous interferon monotherapy, in this multi-center, double-blind, randomized trial: • HCV RNA became undetectable in 34.8 percent of ribavirin patients and 19.6 percent of amantadine patients, however, this was not statistically significant (P=0.10) • Sustained response was maintained in 3.9 percent of ribavirin patients and none of the amantadine patients, however, this was not statistically significant (P=0.16)
Khalili M, et al.[47]	n=29	Alpha-interferon and ribavirin or alpha-interferon and amantadine for 24 weeks	In comparing the potential efficacy and safety of a combination of interferon and ribavirin with that of interferon and amantadine in patients who had previously failed to respond to interferon monotherapy: • At the end of therapy, significantly more patients in the ribavirin group (36%) versus no patients in the amantadine group experienced normal serum alanine aminotransferase and nondetectable HCV RNA by polymerase chain reaction. • After an additional 24 weeks of observation, however, only 15 percent of patients in the ribavirin group achieved a sustained complete response.
Manns MP, et al.[48]	n=1,530	Peginterferon alfa-2b + ribavirin (three dosing regimens) vs. interferon alfa-2b +ribavirin	A sustained virological response (SVR) rate of 41% has been achieved with interferon alfa-2b plus ribavirin. In this randomized trial, peginterferon alfa-2b plus ribavirin was compared with interferon alfa-2b plus ribavirin: • The sustained virological response rate was significantly higher (p=0.01 for both comparisons) in the higher dose peginterferon group (274/511 [54%]) than in the lower dose peginterferon (244/514 [54%]) or interferon (235/505 [47%]) groups. • Among patients with HCV genotype 1 infection, the corresponding sustained virological response rates were 42% (145/348), 34% (118/349), and 33% (114/343). • The rate for patients with genotype 2 and 3 infections was about 80% for all treatment groups. • Secondary analyses identified bodyweight as an important predictor of sustained virological response, prompting comparison of the interferon regimens after adjusting ribavirin for bodyweight (mg/kg) • Side-effect profiles were similar between the treatment groups.

Additional Evidence

Dose Simplification: Several studies were found comparing the efficacy and safety of daily interferon alfa therapy with thrice weekly interferon alfa therapy with or without ribavirin. Multiple studies have found no difference in combination therapy with daily induction treatment compared with combination therapy with thrice weekly dosing.[30, 31, 32] However, one study found that combination therapy is more effective when interferon alfa is administered daily for the first 24 weeks in naïve patients with chronic hepatitis C.[33] Other studies have tried to achieve dose simplification in looking at the duration of therapy. Numerous studies have addressed the efficacy of combination therapy over 24 weeks or 48 weeks. Multiple studies have found that combination therapy with interferon and ribavirin for 48 weeks was more effective than combination therapy for 24 weeks.[34, 35, 36]

Additionally, a study by Kaito et al. that looked at the efficacy of twice-a-day (group A) versus once-a-day (group B) interferon-beta for chronic hepatitis C.[37] The rate of sustained virological response was significantly higher in group A (14 of 22 patients, 63.6%) than in group B (6 of 20 patients, 30.0%) ($p < 0.05$). Among patients with hepatitis C virus-RNA level less than 1 Meq/mL, the sustained virological response rate was significantly higher in group A (13 of 15 patients, 86.7%) than in group B (5 of 12 patients, 41.7%) ($p < 0.05$). In this study, twice-a-day interferon-beta therapy was more effective than once-a-day interferon-beta for the treatment of chronic hepatitis C patients with hepatitis C virus-RNA levels less than 1 Meq/mL.

Stable Therapy: No studies were found utilizing a literature search of Medline regarding changing therapies once stabilized on interferon or peginterferon therapy. However, it is recommended that the specific preparation selected for the patient be used throughout the treatment regimen. This is due to differences in potencies and differences in recommended dosages and routes of administration among the various commercially available interferon alfa and peginterferon alfa preparations.[38]

Impact on Physician Visits: A literature search of Medline did not reveal clinical literature relevant to use of the interferons and their impact on physician visits.

VIII. Conclusions

Interferon alfa-2b / ribavirin (Rebetron) is the only packaged combination therapy for the treatment of hepatitis C. The product does not offer a clinical advantage over the use of other single entity interferons plus the addition of ribavirin (Rebetol or Copegus). In fact, in clinical studies, the pegylated interferons plus ribavirin have shown a more positive impact on the sustained virological response as compared to interferon alfa-2b and interferon alfa-2a plus ribavirin. Treatment guidelines also support the use of the pegylated interferons plus ribavirin for hepatitis C. Additionally, as combination interferon therapy is specifically indicated for hepatitis C, due to this narrow indication and limited use, interferon alfa-2b / ribavirin should be available for special needs/circumstances that require medical justification through the prior authorization process. After clinical circumstances are explored, proper medical justification will provide patient access to these agents.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

IX. Recommendations

No brand combination nucleoside / nucleotide is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Single Entity Urinary Anti-Infectives
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I. Overview

Urinary tract infections (UTI's) are responsible for an estimated 8 million physician office visits and up to 100,000 hospitalizations annually in the United States.[1] The management of UTI's continues to be challenging due to rapidly changing antibiotic susceptibilities in urinary tract pathogens.[1] Proper management of UTI's requires consideration of several factors, including age and sex of the patient, symptoms, underlying disease or catheters, pregnancy, history of prior UTI's, location of infection, and expected pathogen.[1] The urinary anti-infectives included in this review are primarily indicated for uncomplicated acute cystitis and prophylaxis/suppression of recurrent UTI's.

Urinary tract infections are classified by the location of the infection as well as the potential for complications. Generally, the higher up in the urinary tract the infection occurs, the more serious it is. The lower urinary tract consists of the bladder and urethra and infections in those areas are referred to as cystitis and urethritis, respectively. The upper urinary tract is composed of the kidneys and ureters, and infections of the kidney are referred to as pyelonephritis. UTI's are considered simple if they occur in a health urinary tract, do not spread to other parts of the body, and go away readily with treatment. UTI's are considered comp licated if they are caused by anatomic abnormalities, spread to other parts of the body, or are resistant to many antibiotics.[5]

UTI's are more common in adults than in children, although 1-2 % of children present with UTI's.[5] UTI's are more common in women and girls than in men and boys. Approximately 40% of women and 12% of men have a UTI at some point in their lives.[5] Children and men are more likely to present with more serious infections. *E. coli*, which normally lives in the bowel and around the anus, is the causative organism in at least 90% of uncomplicated infections. Conditions that can increase the risk of UTI's include urinary tract obstructions (kidney stones), incomplete bladder emptying, suppression of the immune system, frequent sexual intercourse in women, the diaphragm method of birth control, poor hygiene, catheterization, enlarged prostates in men, and lack of circumcision in men.[5]

Symptoms of cystitis include dysuria, frequency, urgency, hesitancy, lower abdominal pain, mild fever (<101 degrees F), malaise, and cloudy, odorous, or bloody urine.[5] Symptoms of pyelonephritis include high fever (> 101 degrees F), shaking, chills, nausea, vomiting, and flank pain.[5] Symptoms of prostatitis include fever, chills, dysuria, frequency, and urgency. Infants and children may also present with poor feeding, vomiting, hypothermia, jaundice, irritability, and loss of bowel control.[5] The elderly may present with hypothermia, poor appetite, lethargy, or changes in mental status.[5] Diagnosis is generally based upon urinalysis. If a complicated infection is suspected, a urine culture may be necessary. Blood tests and imaging studies are usually reserved for severe pyelonephritis or kidney failure.

This review encompasses all Urinary Anti-Infective dosage forms and strengths.

Table 1. Single Entity Urinary Anti-Infectives in this Review

Generic Name	Formulation	Example Brand Name
Nitrofurantoin, Nitrofurantoin macrocrystals, Nitrofurantoin macrocrystals/monohydrate	Oral suspension, Oral capsules, Oral capsules	Furadantin, *Macrodantin, *Macrobid
Methenamine hippurate	Oral tablets	*Hiprex, Urex
Methenamine mandelate	Oral tablets, Suspension	*Mandelamine
Fosfomycin Tromethamine	Granules	Monurol
Trimethoprim HCL, Trimethoprim	Oral solution (DC 'ed), Oral tablets	Primsol (DC 'ed per manuf), *Proloprim, Trimpex (DC 'ed per manuf)

*Generic Available.

II. Evidence Based Medicine and Current Treatment Guidelines

Acute Uncomplicated Cystitis

The Infectious Diseases Society of America has published guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. In general, single-dose therapy is less effective than a 3 - 7 day regimen of the same anti-microbial. Current standard therapy for the treatment of acute uncomplicated bacterial cystitis is TMP/SMX for three days.[6] Trimethoprim alone and ofloxacin are equivalent to TMP/SMX, with other fluoroquinolones having similar effectiveness.[6] Due to several reasons including the need to postpone resistance to quinolones, they are not recommended for empirical therapy except in situations where resistance to TMP/SMX and trimethoprim alone is known (>10-20%).[6] Beta-lactams are not as effective, but nitrofurantoin and fosfomycin are useful in the case of resistance or inability to tolerate TMP/SMX or trimethoprim alone.

Existing data suggests that nitrofurantoin is less effective than TMP/SMX or trimethoprim alone.[1,5,6,7] However, nitrofurantoin has not shown development of resistance, which allows it a place in therapy in cases of known resistance. Fosfomycin has not shown the same effectiveness as TMP/SMX or trimethoprim alone, but like nitrofurantoin, has a place in therapy in the case of known resistance to TMP/SMX, inability to tolerate or allergy to TMP/SMX, or in pregnancy.

Complicated Cystitis

TMP/SMX and fluoroquinolones are the best empiric therapy for complicated UTI's due to superior tissue and urinary levels.[1] The best length of therapy seems to be 7 - 10 days.

Acute Pyelonephritis

In young, non-pregnant women, 14 days of a fluoroquinolone is the preferred therapy. TMP/SMX is recommended only if susceptibility results are favorable. A 7-day course of therapy may be appropriate for mild to moderate cases.[6] Amoxicillin or amoxicillin/clavulanic acid are alternatives if the causative organism is a gram positive bacterium.[6] Severe infections may require hospitalization and IV antibiotics.

Catheter-Associated Infection

Ciprofloxacin is the drug of choice for nosocomial catheter-associated UTI's.[6] Levofloxacin is an acceptable alternative.[6] Other empiric therapy includes ceftazidime, cefepime, piperacillin, piperacillin/tazobactam, and azetreonam.[6]

Prostatitis

TMP/SMX and trimethoprim alone are alternative treatments. Empiric therapy includes high dose broad-spectrum cephalosporin or an oral fluoroquinolone.

Prophylaxis of Recurrent UTI's

Approximately 25% of women with acute cystitis develop recurrent UTI's.[7] UTI's associated with sexual intercourse can be treated with postcoital prophylaxis regimens of a single dose of nitrofurantoin 50mg, TMP/SMX 40/200mg, or cephalexin 500mg.[7] Prophylaxis regimens for other reasons include TMP/SMX, nitrofurantoin, norfloxacin, and trimethoprim in once daily for thrice weekly dosing.[7] Methenamine also plays a role in the prevention of recurring infections.

III. Comparative Indications of the Single Entity Urinary Anti-infectives

Table 2 lists the microbial indications for the urinary anti-infectives. Table 3 lists FDA-approved indications for the urinary anti-infectives.

Table 2. Microbial indications of the Single Entity Urinary Anti-Infectives[2]

	E. coli	Enterococci	S. aureus	Klebsiella sp.	Enterobacter sp.	P. mirabilis	Staphylococcus sp.	E. faecalis
Nitrofurantoin*	X	X	X	X	X	-	-	-
Methenamine	X	X	-	-	-	-	X	-
Fosfomycin Tromethamine**	X	-	-	-	-	-	-	X
Trimethoprim	X	-	-	X	X	X	X	-

* Nitrofurantoin is not indicated in the treatment of pyelonephritis or perinephric abscesses.

** Fosfomycin is not indicated in the treatment of pyelonephritis or perinephric abscesses.

Table 3. Indications for the Single Entity Urinary Anti-Infectives[2, 4]

Indication	Nitrofurantoin	Methenamine	Fosfomycin Tromethamine	Trimethoprim
Urinary tract infections (UTI)/Acute cystitis	X	-	X	X
Prophylaxis/suppression of UTI	X	X	-	X
Pyelonephritis	-	-	-	-
Catheter associated UTI	-	-	-	-
Prostatitis	-	-	-	X

IV. Pharmacokinetic Parameters of the Single Entity Urinary Anti-Infectives

Table 4 lists the pharmacokinetic parameters and mechanisms of action of the urinary anti-infectives.

Table 4. Pharmacokinetic Parameters of the Single Entity Urinary Anti-Infectives[2, 3]

Drug	Mechanism of Action	Bioavailability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Nitrofurantoin	Bacteriostatic in low concentrations and bacteriocidal in high concentrations. May inhibit acetylcoenzyme A, inferring with bacterial carbohydrate metabolism. May also disrupt bacterial cell wall formation.	Well absorbed from GI tract. Macrocrystalline forms absorb more slowly. Food increased bioavailability.	60%	Body tissues/Liver – 30-50% excreted unchanged in urine.	No	Biliary; <1% eliminated in urine	8-12 hours
Methenamine	Methenamine is hydrolyzed to ammonia and formaldehyde, which is bacteriocidal. Mandelate and hippurate salts help maintain low urine pH.	Readily absorbed, but 10-30% will be hydrolyzed by gastric juices unless enteric coated.	Minimal	Liver (10-25%)	Yes	Feces; <1% eliminated in urine	At least 16 hours
Fosfomycin Tromethamine	Bactericidal. Fosfomycin inactivates enolpyruvyl transferase, which irreversibly blocks the condensation of uridine diphosphate- *N*-acetylglucosamine with phospho *enol*pyruvate, and inhibits bacterial cell wall synthesis. Fosfomycin also decreases the adherence of bacteria to epithelial cells of the urinary tract.	Rapidly absorbed. Bioavailability reduced with food.	No	To free acid fosfomycin. 38% renal elimination 18% fecal.	Yes	Feces; <2% is excreted in urine	
Trimethoprim	Bacteriostatic lipophilic weak base structurally related to pyrimethamine, binds to and	Rapidly absorbed (90-100%)	44%	Liver – (10-20% metabolized). Primarily excreted in kidneys.	No	Renal	0.8-1.5 hours

	reversibly inhibits the bacterial enzyme dihydrofolate reductase, selectively blocking conversion of dihydrofolic acid to its functional form, tetrahydrofolic acid. This depletes folate, an essential cofactor in the biosynthesis of nucleic acids, resulting in interference with bacterial nucleic acid and protein production. Bacterial dihydrofolate reductase is approximately 50,000 to 60,000 times more tightly bound by trimethoprim than by the corresponding mammalian enzyme. Exerts its effect at a step in the folate biosynthesis immediately subsequent to the one in which sulfonamides exert their effect. When administered concurrently with sulfonamides, synergism occurs and is attributed to inhibition of tetrahydrofolate production at two sequential steps in its biosynthesis.			Minimal amounts in feces and bile.			

V. Drug Interactions for the Single Entity Urinary Anti-Infectives

Nitrofurantoin may give false-positive results with copper sulfate reduction tests for urine glucose (Benedict's solution or Fehling's solution). It does not interfere with the glucose enzymatic test.

Methenamine can interfere with laboratory tests for 17-hydroxycorticosteroids, catecholamines, vanillylmandelic acid, 5-hydroxyindolaecetic acid, and urine estradiol.

Table 5. Drug Interactions of the Single Entity Urinary Anti-Infectives[2, 4]

Drug	Significance	Interaction	Mechanism
Nitrofurantoin	Level 3 (delayed, minor, suspected)	Nitrofurantoin and magnesium salts	Adsorption onto magnesium salts may occur, reducing nitrofurantoin bioavailability.
Nitrofurantoin	Level 4 (delayed, moderate, possible)	Nitrofurantoin and hydantoins	Unknown. Serum phenytoin levels may be decreased.
Nitrofurantoin	Level 5 (delayed, minor, unlikely)	Nitrofurantoin and anticholinergics	Delayed gastric emptying by anticholinergics may increase nitrofurantoin bioavailability.
Methenamine	Level 5 (delayed, minor, possible)	Methenamine and alkalinizing agents	Alkalinization counteracts the acidity of formaldehyde, interfering with antibacterial activity.
Fosfomycin Tromethamine	-	Fosfomycin and GI motility drugs	Metoclopramide can lower serum concentration and urinary excretion of fosfomycin.
Trimethoprim	Level 1 (delayed, major, suspected)	Trimethoprim and methotrexate	Both drugs are folate antagonists, therefore trimethoprim may increase risk of methotrexate-induced bone marrow suppression.
Trimethoprim	Level 2 (delayed, moderate, suspected)	Trimethoprim and dapsone	Unknown. Increased serum levels of both drugs may occur.
Trimethoprim	Level 2 (delayed, moderate, probable)	Trimethoprim and hydantoins	Trimethoprim inhibits hepatic metabolism of hydantoins, causing increases in serum hydantoin concentrations.
Trimethoprim	Level 2 (rapid, moderate, suspected)	Trimethoprim and procainamide	Competition for renal tubular cationic secretion may occur, causing elevated procainamide levels.
Trimethoprim	Level 4 (delayed, moderate, possible)	Trimethoprim and amantadine	Inhibited renal clearance of each drug may produce acute mental confusion.
Trimethoprim	Level 4 (rapid, moderate, possible)	Trimethoprim and zidovudine	Decreased renal clearance of zidovudine may cause increased effect of zidovudine. May only be important in patients with impaired liver function.
Trimethoprim	Level 4 (moderate, possible)	Trimethoprim (with SMX) and ethanol	Inhibition of acetaldehyde dehydrogenase may cause a disulfiram-like reaction.
Trimethoprim	Level 4 (delayed, major, possible)	Trimethoprim and cyclosporine	Unknown. Efficacy of cyclosporine may occur along with increased nephrotoxicity.
Trimethoprim	Level 5 (rapid, minor, unlikely)	Trimethoprim and lamivudine	Trimethoprim may inhibit the renal secretion of lamivudine causing increase in lamivudine concentrations.

VI. Adverse Drug Events of the Single Entity Urinary Anti-Infectives

Table 6. Common Adverse Events (%) Reported for the Single Entity Urinary Anti-Infectives[2]

Adverse Event	Nitrofurantoin	Methenamine	Fosfomycin Tromethamine	Trimethoprim
Body as a Whole	-	-	-	-
Malaise	-	-	-	-
Infection	-	-	-	-
Influenza symptoms	-	-	-	-
Moniliasis	-	-	-	-
Myalgia	✔	-	✔	-
Cardiovascular	-	-	-	-
Edema	-	-	-	-
Hypotension	-	-	-	-
Hypertension	-	-	-	-
Chest pain	-	-	-	-
Digestive System	-	-	-	-
Abdominal Pain	✔	✔	2.2	-
Nausea / Vomiting	✔	✔	4.1	✔
Diarrhea	✔	-	9	-
Epigastric distress	-	-	-	✔
Appetite decrease	-	-	-	-
Appetite increase	-	-	-	-
Flatulence	-	-	✔	-
Metallic taste	-	-	-	-
Dry mouth	-	-	✔	-
Anorexia	✔	✔	✔	-
Stomatitis	-	✔	-	-
Dyspepsia	-	-	1.1	-
Constipation	-	-	✔	-
Glossitis	-	-	-	✔
Central Nervous System		-	-	-
Dizziness/Vertigo	✔	-	1.3	-
Fatigue	-	-	-	
Fever	✔	-	✔	✔
Headache	✔	✔	3.9	-
Meningeal Signs	-	-	-	-
Raised Intracranial	-	-	-	-
Pressure	-	-	-	-
Collapse	-	-	-	-
Confusion	✔	-	-	-
Drowsiness	✔	-	-	-
Peripheral Neuropathy	✔	-	-	-
Nystagmus	✔	-	-	-
Depression	✔	-	-	-
Euphoria	✔	-	-	-
Hepatic				
Abnormal LFTs (incr.)	-	-	-	-
Hepatitis	✔	-	-	-
Jaundice	✔	-	-	-
Hepatic failure	-	-	-	-
Skin and Appendages				
Alopecia	-	-	-	-
Rash	-	✔	1.4	✔
Sweat	-	-	-	-
Pruritus	✔	✔	✔	✔
Exfoliative dermatitis	✔	-	-	✔
Skin eruptions	✔	✔	-	✔
Urticaria	✔	✔	-	-
Angioedema	✔	-	-	-
		-		-
Hematologic				
Neutropenia	-	-	-	✔
Agranulocytosis	✔	-	-	-
Anemia	✔	-	-	✔
Thrombocytopenia	✔	-	-	✔
Leukopenia	✔	-	-	✔
	-			
Renal				

Abnormal kidney fxn	-	-	-	✔
Acute kidney failure	-	-	-	-
Metabolic				
Increased creatinine	-	-	-	-
Electrolyte imbalance	-	-	-	-
Hypoglycemia	-	-	-	-
Hypocalcemia	-	-	-	-
GU				-
Vaginitis	-	-	5.5	-
Genital pruritus	-	-	-	-
Abnormal urine	-	-	-	-
Dysmenorrhea	-	-	2.6	-
UTI	-	-	-	-
Dysuria	-	-	✔	-
Proteinuria	-	-	-	-
Hematuria	-	-	✔	-
Crystalluria	-	-	-	-
Respiratory	-			
Rhinitis	-	-	4.5	-
URTI	-	-	-	-
Sinusitis	-	-	-	-
Pharyngitis	-	-	2.5	-
Cough	-	-	-	-
Dyspnea	-	✔	-	-
Other				
Convulsions	-	-	-	-
Back pain	-	-	3	-

✔ Adverse event reported; specific percentages not available.

VII. Dosing and Administration for the Single Entity Urinary Anti-Infectives

Table 7. Dosing for the Single Entity Urinary Anti-Infectives[2, 3]

Drug	Availability	Dose /Frequency/Duration
Nitrofurantoin	25mg/5ml oral suspension Macro/microcrystalline: 25mg, 50mg, 100mg capsules Macrocrystalline/monohydrate form: 100mg (25/75) extended release capsules	**Adults:** 50 to 100mg, 4 times daily with meals and at bedtime for 3 to 7 days or until urine is sterile. Most uncomplicated infections can be treated with 50mg three times daily. If giving 100mg extended release capsules, dose 100mg twice daily for 7 days. Long-term suppressive therapy: 50 to 100mg at bedtime. **Children >1 year:** 5-7 mg/kg/day in 4 divided doses. Long-term suppressive therapy: 1mg/kg/day divided into one or two doses. **Other Notes** • Give with food or milk to improve absorption and tolerance. • May cause brown discoloration of urine.
Methenamine	Hippurate: 1gm tablets Mandelate: 0.5gm, 1gm tablets, 0.5gm, 1gm enteric coated tablets, 0.5gm/5ml suspension, 1gm granules for solution	**Methenamine Hippurate:** Adults and children >12 years: 1gm twice daily Children 6-12 years: 0.5 to 1gm twice daily **Methenamine Mandelate:** Adults: 1gm four times daily after meals and bedtime. Children 6-12 years: 0.5gm four times daily Children <6 years: 0.25gm/14kg four times daily **Other Notes** • Acidifying the urine with ascorbic acid or cranberry juice

		may increase efficacy. • Take with food to minimize GI upset. • Drink plenty of fluids to ensure urine flow. • Avoid alkalinizing foods (milk products) or medications (bicarbonates). • Effectiveness increases in urine pH of 5.5 or below – monitor urine pH.
Fosfomycin Tromethamine	3gm granule packet	**Adults 18 years or older:** One packet mixed in water. **Other Notes** • May be taken with or without food. • Mix packet with 3 to 4 ounces of water (not hot) and stir. • Efficacy does not increase by administering mo re than one packet per acute episode.
Trimethoprim	100mg, 200mg tablets	**Adults and children 12 years or older**: 100mg every 12 hours or 200mg every 24 hours for 10 days.

Special Dosing Considerations

Table 8. Special Dosing Considerations for the Single Entity Urinary Anti-Infectives[2, 3]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed?
Nitrofurantoin	Yes	No	Contraindicated in children less than 1 month of age due to possibility of hemolytic anemia in immature enzyme systems. Safety and efficacy of the macrocrystalline/monohydrate form has not been established in children up to 12 years of age.	B. Do not give at term.	Available in liquid dosage form, which may be mixed with water, milk, fruit juices, or formulas. Do not break, crush, or chew the extended-release macrocrystalline/monohydrate form.
Methenamine	No	No	Dosing recommendations are available for children <6 years old.	C	Available in liquid dosage form.
Fosfomycin Tromethamine	No	No	Safety and efficacy in children <12 years old has not been established.	B	Granules are formulated to mix with water.
Trimethoprim	Yes	No	Safety in children <2 months has not been established. Efficacy in children <12 has not been established.	C	Tablets can be crushed, but there is no information available concerning stability of a compounded liquid formulation per the brand name manufacturer.

VIII. Comparative Effectiveness of the Single Entity Urinary Anti-Infective Agents

Table 9. Additional Outcomes Evidence for the Single Entity Urinary Anti-Infective Agents

Study	Sample	Treatment / Duration	Results
Hooten TM, et al.[8]	n=149	Comparison of 3-day antimicrobial regimens for acute cystitis	In a prospective, randomized trial, 39 women were given either TMP/SMX 160mg/800mg twice daily, macro nitrofurantoin 100mg four times daily, cefadroxil 500mg twice daily, or amoxicillin 500mg three times daily without regard to causative organism: • 82% of TMP/SMX women were cured at 6 weeks compared with 61% of nitrofurantoin, 66% of cefadroxil, and 67% of amoxicillin. • Persistence of significant bacteruria was 3% for TMP/SMX, 0% for cefadroxil, 16% for nitrofurantoin, and 14% for amoxicillin. • Adverse effects were reported in 35% of the TMP/SMX patients, 43% of nitrofurantoin, 30% of cefadroxil, and 25% of amoxicillin. • TMP/SMX appears to be the most effective treatment of the four.
Naber KG, et al.[9]	n=349	Comparison of single-dose therapy of fosfomycin, TMP/SMX, and ofloxacin	Urine cultures of 349 women with acute uncomplicated cystitis were analyzed after single dose therapy of fosfomycin, TMP/SMX, or ofloxacin: • Baseline pathogens were eradicated in 87.1% of fosfomycin patients, 88.9% of TMP/SMX patients, and 86.4% of ofloxacin patients. • Fosfomycin is an equally effective single-dose therapy agent.
Naber KG, et al.[10]	n=562	Comparison of single-dose therapy of fosfomycin, TMP/SMX, and ofloxacin	562 patients with acute uncomplicated UTI were randomized to receive either a single dose of fosfomycin, ofloxacin, or TMP/SMX: • In patients with "significant" bacteriuria, clinical improvement was attained in 97.7% of fosfomycin patients, 95.4% of ofloxacin patients, and 94% of TMP/SMX patients. • In patients with "low count" bacteriuria, clinical improvement was attained in 95.2% of fosfomycin patients, 93.7% ofloxacin patients, and 96.4% of TMP/SMX patients. • In patients with no bacteriuria, clinical improvement was attained in 81.8% of fosfomycin patients, 100% of ofloxacin patients, and 100% TMP/SMX patients.
Pienbroek E, et al.[13]	n=231	Single dose of fosfomycin 3gm versus nitrofurantoin 50mg four times daily for 7 days	231 patients with acute, uncomplicated cystitis were evaluated in a randomized, double-blind trial: • Clinical cure rates and bacteriological cure rates were not significantly different between the two groups. • There was a significant difference in side effects reported, by day 4 – 43% of fosfomycin patients vs. 25% of nitrofurantoin patients. • The side effects were mild and GI complaints were the most common. • A single dose of fosfomycin is as effective as 7 days of nitrofurantoin, although there was a higher frequency of mild side effects.
Brumfitt W, et al.[14]	n=72	Long-term prophylaxis with Macrodantin vs. trimethoprim	72 patients with a history of at least three UTI's within the previous 12 months were randomly assigned to either Macrodantin 100mg at bedtime or trimethoprim: • The mean interval between attacks was increased three-fold on both treatments. • Macrodantin was significantly more effective at preventing bacteriuria. • Side effects were significantly more common in the Macrodantin group. • Acquisition of resistance was higher in the trimethoprim group.
Junnila KA, et al.[15]	n=290	Methenamine hippurate vs. nitrofurantoin vs. trimethoprim vs. placebo in secondary prevention	290 patients with recurrent UTI were treated with either placebo, methenamine hippurate, nitrofurantoin, or trimethoprim: • 63.2% recurred in the placebo group, 34.2% in the methenamine hippurate group, 25% in the nitrofurantoin group, and 10.4% in the trimethoprim group. • Side effects were mild and occurred most frequently in the nitrofurantoin group (13.9%)

Cronberg S, et al.[16]	n=21	Methenamine hippurate vs. placebo for prevention of recurrent cystitis	In this double-blind, randomized, crossover study of 21 patients, methenamine hippurate and placebo were interchanged every six months for two years: • Of the 52 episodes of acute cystitis caused by reinfection, 41 occurred during placebo and 11 during the methenamine regimen. • Methenamine is an effective agent against recurrent cystitis without the incidence of resistance of other anti-infectives.
Brumfitt W, et al.[17]	n=99	Nitrofurantoin vs. methenamine hippurate for prevention of recurrent cystitis	99 patients with recurrent UTI's were given either 1gm methenamine hippurate every 12 hours or 50mg nitrofurantoin every 12 hours, for intervals of up to one year: • Both treatments were effective in reducing the incidence of symptomatic attacks, with nitrofurantoin being more effective. • Methenamine was better tolerated than nitrofurantoin, especially during the first month of treatment, primarily due to nausea.

Additional Evidence

Dose Simplification: In most cases, the urinary anti-infective agents in this class are given as a single dose, or for a brief duration (acute use). Even in the case of prophylactic or suppressive therapy, dosing is generally once daily or three times per week. The most cumbersome dosing regimen in the class is four times daily dosing of nitrofurantoin, which can be alleviated in adults by prescribing the twice-daily extended release capsule dosage form. Studies presented show fosfomycin (single dose) is as effective as nitrofurantoin and TMP/SMX in treating uncomplicated urinary tract infections/cystitis, with a higher incidence of adverse events in the fosfomycin treated patients.

Stable Therapy: Significant evidence exists concerning the development of trimethoprim-resistant strains amongst organisms that cause UTI's. Nitrofurantoin and fosfomycin are considered alternative therapies in the case of known trimethoprim resistance or intolerance to TMP/SMX or trimethoprim therapy.

Nitrofurantoin's unique mechanism of action, and the fact that it interferes with a variety of bacterial processes, may explain the lack of acquired bacterial resistance to nitrofurantoin.[3] However, due to lack of broad tissue distribution, many patients treated with nitrofurantoin are predisposed to persistence or reappearance of bacteruria.[3]

Fosfomycin generally exhibits no cross-resistance with other classes of antibacterial agents, such as beta-lactams and aminoglycosides.

Impact on Physician Visits: Urinary tract infections are responsible for an estimated eight million physician office visits and up to 100,000 hospitalizations annually in the U.S.[1] The challenge in the treatment of urinary tract infections lies in choosing the medication that the causative organism is not resistant to, but not overusing broad spectrum agents to which resistance can develop. In a study published in the Annals of Epidemiology, insurance claims were analyzed retrospectively to determine if length of therapy prescribed matched that of recommendations in published guidelines. It was determined that the first line recommended agent, TMP/SMX, was prescribed in only 37% of acute infections, and for considerably longer than the suggested 3-day course, with the mean duration being ten days regardless of whether the infection was acute or recurrent.[12]

In a study published in the American Journal of Medicine, the effectiveness of clinical practice guidelines for the management of uncomplicated UTI in women was observed. The study measured the return rate of 3,889 patients with cystitis or sexually transmitted disease or who developed pyelonephritis within 60 days. As compared with baseline, guideline implementation significantly decreased the proportion of patients with presumed cystitis who received urinalysis, urine culture, and an initial office visit while increasing the proportion who received a guideline-recommended antibiotic 2.9 fold.[11]

IX. Conclusions

Nitrofurantoin is an effective alternative to the empiric therapy of TMP/SMX (not included in this review), trimethoprim alone, or a quinolone in the treatment of uncomplicated cystitis or the prevention of recurrent episodes. Nitrofurantoin may be slightly less effective than empiric therapy, but offers an advantage in the case of drug allergy, intolerance, or microbial resistance. All capsule formulations of nitrofurantoin are available generically, but the liquid formulation is not. Liquid nitrofurantoin should be reserved for special needs, through medical justification through the prior authorization program.

Fosfomycin has been shown to be as effective, and is an alternative therapy, to the empiric therapy of TMP/SMX, trimethoprim alone, or a quinolone in the treatment of uncomplicated cystitis; and like nitrofurantoin, has an advantage over empiric therapy in the case of intolerance or resistance. Fosfomycin is not available generically.

Trimethoprim is considered empiric therapy in the treatment of uncomplicated UTI alone or in combination with SMX. It is also recommended in the prevention of recurrent UTI's. However, the rate of resistance to trimethoprim is high. Trimethoprim is not available in liquid form, but is available generically in tablet form.

Methenamine is a reasonable alternative therapy to nitrofurantoin, TMP/SMX, and cephalexin in the prevention of recurrent UTI's. Although methenamine has been shown to be slightly less effective than empiric therapy, it is usually better tolerated and shows less incidence of resistance. Methenamine is available generically.

Therefore, all single entity brands within the class are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand single entity urinary anti-infective is recommended for preferred status.

Pharmacotherapy Review of the Combination Urinaty Anti-Infective Combination Agents
AHFS 083600

I. Comparative Indications of the Urinary Anti-Infective Combination Agents

This review encompasses all Urinary Anti-Infective Combination dosage forms and strengths.

Table 1. Urinary Anti-Infective Combinations in this Review

Generic Name	Formulation	Example Brand Name (s)	Rx vs. OTC
ATP/BA/HYOS/ME BLU/MTH/SAL	Oral tablet	Prosed/DS*, Prosed EC, Trac 2X, Urised*	RX
HYOS/ME BLU/MTH/NA PHOS/SAL	Oral tablet	Urelle, Urimar-T*, Urimax*, UTA, Utira*, Uro Blue	RX
Methenamine/hyoscyamine	Oral tablet	Urisedamine	RX
Methenamine/Na Phos	Oral tablet	Uroquid-Acid #2	RX
MTH/SAL/BA	Oral tablet	Cystex	OTC

*Generic Available

II. Evidence Based Medicine and Current Treatment Guidelines

Accepted indications of the urinary antiseptic combination products include relief of local symptoms, such as inflammation, hypermotility, and pain, which accompany lower urinary tract infections.[3] They are also indicated for the relief of urinary tract symptoms caused by diagnostic procedures.[3] Although there is also a labeled indication for the treatment of cystitis and in the prevention of recurrent UTI's, these drugs are generally recommended only for the treatment of symptoms, or after acute infection has been destroyed by other agents.[3] Uroquid Acid No. 2 and Urisedamine are the exceptions to this, since they each contain 0.5gm methenamine per tablet, allowing for dosages appropriate for the prevention of recurrent UTI's.

No additional guideline information was found in a search of Medline, Ovid, and other medical resources on the internet.

III. Pharmacokinetic Parameters

Table 2 lists the pharmacokinetic parameters and mechanisms of action of each of the components of the urinary anti-infective combinations.

Table 2. Pharmacokinetic Parameters of the Components of Urinary Anti-Infective Combination Products [3]

Drug	Mechanism of Action	Bio-availability	Protein Binding	Metabol-ism	Active Metabol-ites	Elimination	Half-Life
Atropine	Relax smooth muscle spasm by inhibiting the muscarinic actions of acetylcholine on autonomic effectors innervated by postganglionic cholinergic nerves as well as on smooth muscle.	Well absorbed. 30-50% excreted unchanged in urine.	Moderate	Liver	No	Biliary; <1% eliminated in urine	8-12 hours
Hyoscyamine	Relax smooth muscle spasm by inhibiting the muscarinic actions of acetylcholine on autonomic effectors innervated by postganglionic cholinergic nerves as well as on smooth muscle.	Well absorbed. Majority excreted unchanged in urine.	Moderate	Liver	No		
Methenamine	Methenamine is hydrolyzed to ammonia and formaldehyde, which is bacteriocidal. Mandelate and hippurate salts help maintain low urine pH.	Readily absorbed, but 10-30% will be hydrolyzed by gastric juices unless enteric coated.	Minimal	Liver (10-25%)	Yes	Feces; <1% eliminated in urine	At least 16 hours
Methylene blue	Mild antiseptic. May inhibit bacterial proliferation. Ineffective in the treatment of UTI's	Well absorbed. 75% excreted unchanged in urine.	-	Tissues	Yes	Feces; <2% is excreted in urine	
Benzoic acid	Mild	Well	-	Liver	-	Renal	0.8-1.5 hours

	antibacterial and antifungal action. Also helps maintain an acid urine pH necessary for the degradation of methenamine.	absorbed.					
Phenyl salicylate	Produces analgesia through a peripheral action by blocking pain impulse generation via a central action, possibly the hypothalamus.	Well absorbed.	-	-	-		

IV. Drug Interactions

Because of atropine and hyoscyamine effects on GI motility and gastric emptying, absorption of other oral medications may be decreased with concurrent use.

Table 3. Drug Interactions of the Urinary Anti-Infective Combination Products[3]

Drug	Significance	Interaction	Mechanism
Atropine Hyoscyamine	Level 2 (delayed, moderate, suspected)	Anticholinergics and phenothiazines	Therapeutic effects of phenothiazines may be decreased.
Atropine Hyoscyamine	Level 4 (delayed, moderate, possible)	Anticholinergics and digoxin	Digoxin serum levels may increase in the case of slow-dissolution tablets.
Atropine Hyoscyamine	Level 5 (delayed, minor, unlikely)	Anticholinergics and nitrofurantoin	Delayed gastric emptying by anticholinergics may increase nitrofurantoin bioavailability.
Atropine Hyoscyamine	Level 4 (rapid, moderate, possible)	Anticholinergics and beta-blockers	Bioavailability of atenolol may be increased.
Atropine Hyoscyamine	Level 4 (delayed, moderate, possible)	Anticholinergics and amantadine	Synergistic mechanisms may lead to increased side effects of both.
Atropine Hyoscyamine	Level 5 (rapid, minor, possible)	Anticholinergics and acetaminophen	Slight delay in absorption, which should not decrease effectiveness of acetaminophen.
Methenamine	Level 5 (delayed, minor, possible)	Methenamine and alkalinizing agents	Alkalinization counteracts the acidity of formaldehyde, interfering with antibacterial activity.

V. Adverse Drug Events of the Urinary Anti-Infective Combination Products

The majority of the side effects associated with the urinary combination products are due to the anticholinergic effects of atropine and hyoscyamine. Reported side effects include blurred vision, increased intraocular pressure, dizziness, difficult urination, nausea or vomiting, stomach pain, and blue or green urine and/or stools.[3] Methylene blue can cause a false–positive result with the Hemoccult fecal blood test.

VI. Dosing and Administration for the Urinary Anti-Infective Combination Products

- Acidifying the urine with ascorbic acid or cranberry juice may increase efficacy.
- May discolor urine and/or stools.
- Drink plenty of fluids to ensure urine flow.
- Avoid alkalinizing foods (milk products) or medications (bicarbonates).
- Effectiveness increases in urine pH of 5.5 or below; monitor urine pH.

Table 4. Dosing for the Urinary Anti-Infective Combination Products[2]

Drug	Availability	Dose /Frequency/Duration
Trac Tabs 2X	Oral tablets	**Adults:** 1 or 2 tablets four times daily. • Pediatric dosing not specified.
Urelle	Oral Tablets	**Adults:** 1 tablet four times daily followed by liberal fluid intake. **Older children:** Individualize dose.
Prosed/DS	Oral Tablets	**Adults:** 1 tablet four times daily • Pediatric dosing not specified.
Uro Blue Urogesic Blue	Oral Tablets	**Adults:** 1 tablet four times daily followed by liberal fluid intake. • Pediatric dosing not specified.
Urimax	Delayed release tablets	**Adults:** 1 tablet four times daily • Pediatric dosing not specified.
Urimar-T	Oral tablets	**Adults:** 1 tablet four times daily • Pediatric dosing not specified.
Uroquid-Acid No. 2	Oral tablets	**Adults: Initial dose:** 2 tablets four times daily **Maintenance dose**: 2 - 4 tablets daily in divided doses. • Pediatric dosing not specified
Urisedamine	Oral tablets	**Adults:** 2 tablets four times daily **Children 6 years or older:** Reduce dose in proportion to age and weight.
Urinary Antiseptic Urised	Oral tablets	**Adults:** 2 tablets four times daily **Children 6 years or older:** Reduce dose in proportion to age and weight.
MHP-A	Oral tablets	**Adults:** 2 tablets four times daily **Children 6 years or older:** Reduce dose in proportion to age and weight.
Uriseptic	Oral tablets	**Adults:** 2 tablets four times daily with liberal fluid intake. **Children 6 years or older:** Reduce dose in proportion to age and weight.
Cystex	Oral tablets	**Adults and children >16 years old:** 2 tablets four times daily with meals and bedtime.

Special Dosing Considerations

Table 5. Special Dosing Considerations for the Urinary Anti-Infective Combination Products [3]

Drug	Renal Dosing?	Hepatic Dosing?	Pediatric Use	Pregnancy Category	Can Drug Be Crushed?
All urinary combination products	No	No	Generally not recommended in children due to increased likelihood of toxicity with anticholinergics.	C	Information is not available concerning the crushing of tablets. Should be avoided in extended-release dosage forms.

VII. Comparative Effectiveness of the Urinary Anti-Infective Agents

No studies were found in Medline or Ovid that compared the effectiveness of the combination urinary tract anti-infectives to each other or to other single entity agents.

Additional Evidence

Dose Simplification: In most cases, the urinary anti-infective agents in this class are given for a brief duration (acute use). Each of the products in this group are dosed four times daily. Since their recommended use is unique from other products (sulfa and quinolone antibiotics), dose simplification does not apply.

Stable Therapy: A literature search of Medline and Ovid did not reveal data pertinent to the urinary anti-infective combination agents and stable therapy.

Impact on Physician Visits: Urinary tract infections are responsible for an estimated eight million physician office visits and up to 100,000 hospitalizations annually in the U.S.[1] No further clinical literature was found in a search of Medline or Ovid regarding the combination anti-infective agents and any impact on physician visits.

VIII. Conclusions

Very little evidence is available concerning the comparative effectiveness of the urinary anti-infective combination products in a search of both Medline and Ovid. Each product differs in exact ingredients, however, all of the products have low-dose (40mg -120mg) methenamine in common, with the exception of Uroquid-Acid No. 2 and Urisedamine, which each have the higher dose of 500mg. Generic and OTC combination urinary anti-infectives are available.

Therefore, all brand products within the class are comparable to each other and to the generics and OTC products and offer no significant clinical advantage over other alternatives in general use.

IX. Recommendations

No brand urinary anti-infective combination product is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review-
Fortamet® (metformin extended-release)
Biguanides, AHFS Class 682004
January 26, 2005

I. Overview

Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels. The disorder can be classified as either Type 1 (insulin dependent) or Type 2 (non-insulin dependent) diabetes. Other less common forms of diabetes are gestational diabetes, drug-induced diabetes, and immune-mediated diabetes. Diagnosis today is based on pathogenesis and clinical presentation rather than age of onset. Ninety percent of diabetics have Type 2 disease, which can be reflective of physical inactivity and other lifestyle characteristics.[1] In Type 2 diabetes, although endogenous insulin is present, plasma insulin concentrations may be decreased, increased or normal. Glucose-stimulated secretion of endogenous insulin is frequently reduced, and decreased peripheral sensitivity to insulin is almost always associated with glucose intolerance. In comparison, Type 1 diabetes results from autoimmune destruction of the pancreatic β-cell, responding to insulin replacement therapy to restore deficient levels of endogenous insulin and temporarily restore the ability of the body to properly utilize carbohydrates, fats, and proteins. Obesity may be a confounder as overlapping insulin resistance with β-cell dysfunction may result in diabetes.

Nearly 16 million Americans (7% of the population) have diabetes and there is likely one person undiagnosed for every two persons currently diagnosed with the disease.[1] In 2002, antidiabetic medications accounted for 208 prescriptions per 1000 national Medicaid members.[2] Uncontrolled diabetes results in microvascular, macrovascular and neuropathic complications. This disease is the leading cause of blindness in adults and is the leading contributor to the development of end-stage renal disease. Additional metabolic abnormalities commonly seen in diabetic patients include obesity, hypertension, hyperlipidemia, and impaired fibrinolysis. Epidemiologic data indicate that the incidence of obesity in children with Type 2 diabetes is increasing such that 8%-45% of children with newly diagnosed diabetes have nonimmune-mediated diabetes mellitus.[2]

Although Type 1 diabetes is likely initiated by the exposure of a genetically susceptible individual to an environmental agent, Type 2 diabetes is a heterogenous disorder with multiple risk factors.[3] Risk factors for the development of Type 2 diabetes include:

- Family history (parents or siblings with diabetes)
- Obesity (>20% over ideal body weight or BMI $\geq$27kg/m^2)
- Habitual physical inactivity
- Age, gender, and certain ethnic groups are risk factors
- Previously identified impaired glucose tolerance or impaired fasting glucose
- Hypertension ($\geq$ 140/90mmHg)
- HDL cholesterol $\leq$ 35mg/dL and/or a triglyceride level $\geq$ 250mg/dL
- History of gestational diabetes or delivery of a baby >9 pounds
- Polycystic ovary disease

Proper treatment, both pharmacological and non-pharmacological with lifestyle modifications, can reduce cardiovascular mortality, mortality from other diabetic complications, and help diabetic patients live healthier, longer lives.

The biguanide AHFS class was originally reviewed in August 2004. The original review of the biguanide products is available in full for reference in Appendix A. Fortamet® is a metformin extended-release product. This review encompasses all dosage forms and strengths.

II. Current Treatment Guidelines

United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS diabetes initiative, started in 1977, was a multi-center, randomized, controlled intervention trial, comparing treatment with conventional diet-based blood glucose control therapy or intensive pharmacotherapy with a sulfonylurea, insulin, or metformin. The primary goal of the study was to determine if glycemic control in Type 2 diabetes prevents diabetic complications and their associated morbidity and mortality. The study included various subsets, looking at blood pressure control and efficacy of combination pharmacotherapy treatments. Results from the trial were published in 1998 and involved 3,867 newly diagnosed Type 2 diabetic patients.[4] The study provided definitive evidence for the benefit of intensive management of blood glucose level and blood pressure in patients with Type 2 diabetes.[5] Subset studies from UKPDS have published other important data regarding treatment of Type 2 diabetic patients. In addition, the Diabetes Control and Complications Trial (DCCT), the "sister" study to UKPDS for Type 1 diabetes, also produced support in favor of intensive treatment.

Diabetes Control and Complications Trial (DCCT)

In this trial, patients were randomized to intensive treatment (3-4 insulin injections or continuous subcutaneous insulin infusion, plus home blood glucose monitoring) or conventional treatment (1-2 insulin injections plus home urine glucose testing and blood glucose testing).[6] In evaluating the effect of hyperglycemia on the microvascular complications of Type 1 diabetes, intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared to conventional treatment. Other outcomes of DCCT included:

- Absolute risks of retinopathy and nephropathy were proportional to the mean HbA1c over the follow-up period preceding the event.
- Intensive treatment was most effective when begun early, before complications were detectable, and the rate of progression of complications remained less for the intensive group.
- Nocturnal hypoglycemia can be a barrier for patients to achieve goal glycemic control.
- The benefits of intensive treatment extended well beyond the period of the most intensive implementation.

Treatment Guidelines and Recommendations

American Diabetes Association[7]

1. Diagnosis of Diabetes Mellitus*:
   - Symptoms of diabetes plus casual plasma glucose concentration ≥200mg/dl (11.1mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. OR
   - FPG ≥126mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8h. OR
   - 2-h postload glucose ≥200mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

   *In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

2. Introduction of pre-diabetes as defined by the following diagnosis criteria: Patients with impaired fasting glucose and/or impaired glucose tolerance are referred to as having "pre-diabetes," indicating high risk for the development of diabetes.
   Fasting plasma glucose
   <100mg/dl = normal fasting glucose
   100-125mg/dl = impaired fasting glucose
   ≥ 126mg/dl = provisional diagnosis of diabetes, with confirmation

   Oral glucose tolerance test
   2-h postload glucose <140mg/dl = normal glucose tolerance
   2-h postload glucose 140-199mg/dl = impaired glucose tolerance
   2-h postload glucose ≥ 200mg/dl = provisional diagnosis of diabetes, with confirmation

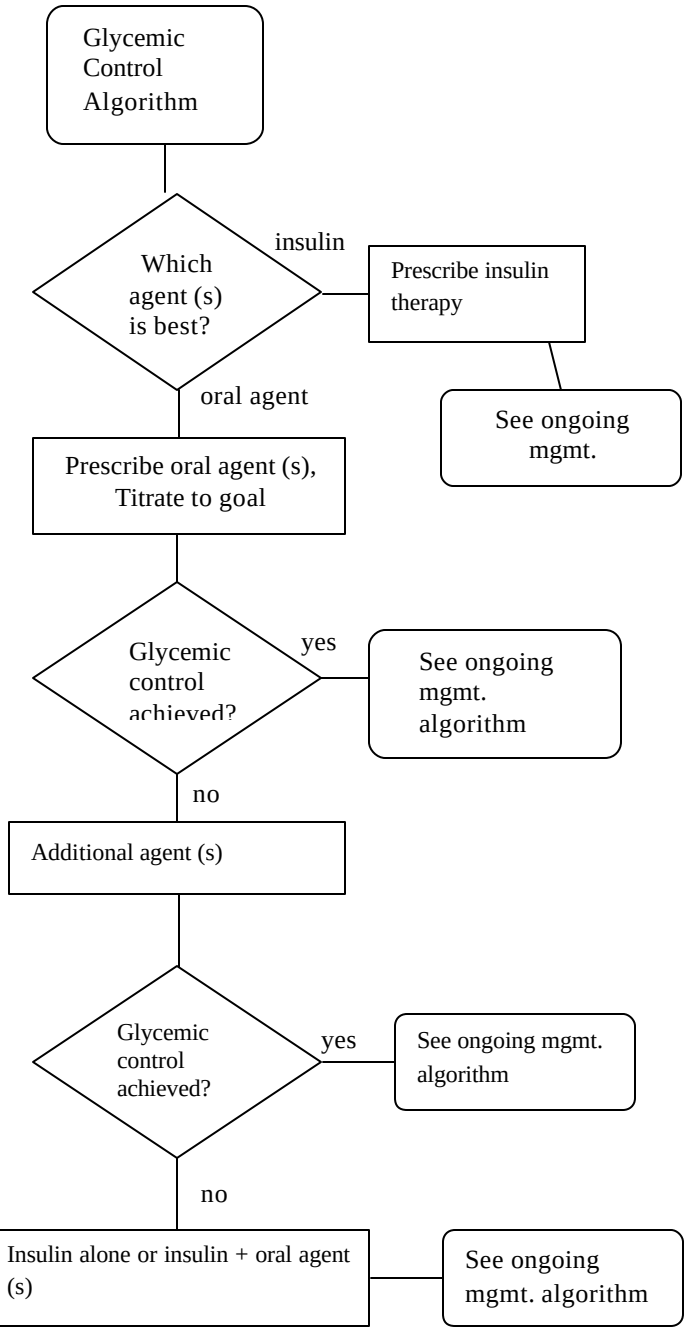
3. Standards of care as revised in the 2004 Clinical Practice Recommendations:
   - HgA1c: <7.0% (nondiabetic range is 4%-6%), however, more stringent goals can be considered in individual patients based on epidemiological analyses suggesting there is no lower limit of HgA1c at which further lowering does not reduce the risk of complications. However, this may increase the risk of hypoglycemia in those patients.
   - Preprandial plasma glucose: 90-130mg/dl
   - Postprandial plasma glucose: <180mg/dl
   - Blood pressure: <130/80mmHg (based on ALLHAT), treatment with an ACEI or ARB is recommended
   - LDL cholesterol: <100mg/dl
   - Triglycerides: <150mg/dl
   - HDL: >40mg/dl
   - Total cholesterol: Diabetic patients over age 40, with a level of ≥135mg/dl, should receive statin therapy to achieve an LDL reduction of approximately 30%, regardless of baseline LDL levels.
   - Anti-platelet: Aspirin therapy is recommended as primary and secondary therapy at a dose of 75-162mg/day. Plavix can be considered in aspirin-intolerant patients.
4. Pharmacological Treatment:
   Diagnosis →Therapeutic lifestyle changes→Monotherapy with oral agents →Combination therapy with oral agents→Combination therapy with oral plus insulin therapy.

The American Association of Clinical Endocrinologists (AACE)[8]
1. A multidisciplinary approach to the treatment of diabetes should include a health-care team consisting of a clinical endocrinologist, diabetes-trained nurse, certified diabetes educator, pharmacist, psychologist and an exercise physiologist. 2. Intensive therapy should be initiated for both Type 1 and Type 2 diabetics. Intensive therapy is defined as a comprehensive program of diabetes care that includes, as two of its components, frequent self-monitoring of blood glucose levels and more complex and sophisticated regimens for maintaining near-normal glucose levels. 3. Type 1: Intensive treatment for Type 1 diabetics likely includes multiple insulin injections daily or subcutaneous insulin infusion therapy. 4. Type 2: Intensive treatment for Type 2 diabetics should not be based on trial-and-error. The cornerstone for Type 2 diabetes treatment is proper diet, exercise and education. Once a nutrition and exercise program have been initiated, oral medications can be given if needed. Choices for initial oral agents should be based on desired outcome, individual response, and side effect profiles. The clinical endocrinologist should lead the team in clinical judgments pertaining to the best combinations of medications for each individual patient. 5. Proper treatment of comorbid conditions is critically important for achieving optimal outcomes in patients with diabetes mellitus. 6. The AACE guidelines stress tighter control of blood glucose in both Type 1 and Type 2 diabetics for significant reductions in the development and progression of microvascular complications (per DCCT and UKPDS). 7. Finally, AACE recommends management of diabetes mellitus through a patient-physician contract, defining both the patient and physician responsibilities.

Institute for Clinical Systems Improvement[9]
1. Clinical Highlights: • Focus on cardiovascular risk reduction (blood pressure, lipids, ASA, and tobacco cessation). ACE inhibitors and ARBs are preferred first-line agents; however, combination therapy should include thiazide diuretics. • Glycemic control of less than 7% often required frequent drug intensification and use of combination therapy. See glycemic control algorithm on page 6. • Aggressive blood pressure control is just as important as glycemic control. Systolic blood pressure level should be the major factor for detection, evaluation, and treatment of hypertension. This may require the use of two or more agents (to include thiazide diuretics). • Self-management support (includes nutrition therapy, physical therapy, education for self management, foot care and community resources) is necessary for people with diabetes to manage their disease. • Prevent microvascular complications through annual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. 2. Treatment Goals for Individuals: • HbA1c: <7% • Blood pressure control: <130/80mmHg • Lipid levels: LDL<100mg/dl • ASA / antiplatelet medication unless contraindicated • Tobacco cessation if indicated 3. Maintain Treatment Goals: Monitor HbA1c every 3-6 months — Monitor lipid profile yearly Monitor blood pressure at each visit — Stress proper nutrition and exercise 4. Annual Assessment of complications: Targeted history and physical exam — Specialist dilated eye exam Renal assessment — Comprehensive foot exam Cardiovascular and cerebrovascular complication assessment Special considerations

Institute for Clinical Systems Improvement cont'd[9]

Glycemic Control Algorithm



Information for ongoing management algorithms is available at www.icsi.org.

III. Indications

The metformin (Fortamet®) extended-release tablets are indicated for use as a once per day monotherapy, and as an adjunct to diet and exercise, to lower blood glucose.[10,11] The drug can be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults. This metformin extended-release formulation is indicated in patients 17 years of age and older as either monotherapy or in combination therapy. Metformin extended-release has the same contraindications as with immediate-release metformin.

IV. Pharmacokinetics

Absorption
Metformin absorbed from the Fortamet® extended-release tablet is slower and more prolonged compared to immediate-release metformin tablets.[10] The effect is a smooth and sustained release of drug for extended glycemic control, achieved with a true once-a-day dose.[13] Metformin extended-release provides a consistent and predictable dose-associated increase in metformin exposure. Studies using oral doses of immediate-release metformin tablets of 500mg to 1,500mg and 850mg to 2,550mg, indicate there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. In a multi-dose cross-over study, 23 patients with Type 2 diabetes were given either metformin extended-release 2,000mg QD or immediate-release metformin 1,000mg BID. Table 1 compares the pharmacokinetic parameters of the different metformin release products administered in this four week study.

Table 1. Metformin Extended-Release (Fortamet®) vs. Immediate-Release Metformin

Pharmacokinetic Parameters (mean +/- SD)	Metformin extended-release 2,000mg QD (administered after dinner)	Immediate-Release Metformin 2,000mg (1,000mg BID)
AUC 0-24hr (ng·hr/ml)	26,811 ± 7055	27,371 ± 5,781
Tmax (hr)	6 (3-10)	3 (1-8)
Cmax (ng/ml)	2849 ± 797	1820 ± 370

In multiple single-dose studies, the bioavailability of metformin extended-release (Fortamet®) was similar to the same total daily dose administered as immediate-release metformin.[10] The extent of metformin absorption from metformin extended-release is increased by 60% when given with food. When given with food, Cmax was increased by approximately 30% and Tmax was more prolonged compared with the fasting state (6.1 vs. 4.0 hours).

In a single-dose, four period replicate crossover study comparing two 500mg metformin extended-release tablets to one 1000mg metformin extended-release tablet, the two 500mg metformin extended-release tablets were found to be equivalent to one 1000mg metformin extended-release tablet.[13]

Distribution
Distribution studies with metformin extended-release have not been conducted.

Metabolism and Excretion
Metabolism studies with metformin extended-release (Fortamet®) have not been conducted. The percentage of metformin from Fortamet® excreted in the urine over 24 hours is 40.9% and renal clearance is 542 ± 310 ml/min.[10] After repeated administration, there is little or no accumulation of metformin in plasma, with most of the drug being eliminated by renal excretion over a 24-hour interval. The half-life of metformin extended-release is 5.4 hours.

V. Drug Interactions

Drug interactions reported in the package insert for metformin extended-release are based on clinical evaluations of drug interactions conducted with immediate-release metformin.

Multiple studies have documented interactions with the biguanide medications. Cationic drugs (amiloride, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.[11] This type of interaction has been documented specifically with cimetidine, where there was a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin area under the curve (AUC). Careful monitoring and dosage adjustments with metformin may be necessary.

Metformin also interacts with certain drugs known to produce hyperglycemia, leading to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. Close monitoring is necessary when these drugs are added or removed from treatment protocols of diabetic patients. Table 2 is a description of the clinically significant biguanide drug interactions with ratings of Level 1 and 2 (moderate or major, suspected). Other less significant documented interactions with metformin include: acarbose, atropine, belladonna, benztropine, biperiden, dicyclomine, hyoscyamine, oxybutynin, procyclidine and propantheline.

Table 2. Clinically Significant Drug Interactions [12]

Significance	Interaction	Mechanism
1	Metformin and Iodinated Contrast Materials, Parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin, resulting in increased risk of metformin-induced lactic acidosis. Co-administration is contraindicated; metformin should be temporarily stopped for purposes of the procedure.
2	Metformin and Cimetidine	Cimetidine reduces the renal clearance of metformin by inhibiting renal tubular secretion. Serum concentrations of metformin may be elevated, increasing the pharmacologic effects. Metformin dosage adjustments may be necessary when cimetidine is stopped or started.

VI. Adverse Drug Events

In studies, the most frequently reported adverse events with metformin extended-release are infection, diarrhea, and nausea.[10] Similar incidences of these events have been reported with immediate-release metformin. Other frequent adverse events thought to be related to metformin extended-release are dyspepsia, flatulence, and abdominal pain. The frequency of flatulence was 3.5% with metformin extended-release compared with 3.7% in the immediate-release metformin group, while the frequency of abdominal pain was 3.3% with metformin extended-release and 4.4% with immediate-release metformin. In one comparative trial, 4.7% of patients treated with metformin extended-release (Fortamet®) and 4.9% of patients treated with immediate-release metformin were discontinued due to adverse events.[10] Additionally, in the same trial, there was an 18% lower incidence of diarrhea associated with metformin extended-release (15.2% with 1000mg BID of immediate-release metformin versus 12.5% with 2000mg QD of metformin extended-release).[13]

More data on the adverse events specifically for immediate-release metformin is available in the Fortamet® package insert, and as described in the previous biguanide review. Table 3 compares the common adverse events with metformin extended-release and immediate-release metformin.

Table 3. Adverse Events (Incidence = 5%) with Metformin Extended-Release (Fortamet®) and Immediate-Release Metformin[10, 13*]

	Metformin Extended-Release (n=424)		Immediate-Release Metformin	
Adverse Reaction	**n**	**(%)**	**n**	**(%)**
Body as a Whole				
Accidental Injury	31	(7.3)	24	(5.6)
Headache	20	(4.7)	22	(5.1)
Infection	87	(20.5)	90	(20.9)
Digestive System				
Diarrhea	71	(16.7)	51	(11.9)
Dyspepsia	18	(4.2)	22	(5.1)
Nausea	36	(8.5)	32	(7.4)
Respiratory System				
Rhinitis	18	(4.2)	24	(5.6)

*Number and percentage of patients with the most common (incidence = 5%) treatment emergent signs and symptoms by body system and Phase II and III studies.

Lactic Acidosis

Lactic Acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during therapy. Lactic acidosis can be fatal in approximately 50% of cases. The reported cases of lactic acidosis in patients receiving metformin is very low (0.03 cases/1000 patient-years, with 0.015 fatal cases/1000 patient-years).[13] Cases typically have occurred in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, and in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The risk of lactic acidosis increases with the degree of renal dysfunction and with patient age. Risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin extended-release, and by use of the minimum effective dose.

Metformin extended-release should not be initiated in patients = 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced. Metformin extended-release should be withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

Lactic acidosis is a medical emergency that requires hospitalization. Metformin extended-release should be discontinued and supportive measures instituted. Metformin is dialyzable with prompt hemodialysis is recommended to correct the acidosis and remove metformin.

VII. Dosing and Administration

Fortamet® (metformin extended-release) is available in 500mg and 1,000mg tablets. This metformin extended-release product, therefore, offers the only 1,000mg extended-release metformin tablet on the market. Additionally, absorption of metformin extended-release (Fortamet®) increases with food, unlike other metformin formulations.[13]

The metformin extended-release (Fortamet®) tablet consists of an osmotically active core formulation that his surrounded by a semipermeable membrane.[13] There are two laser drilled exit ports in the membrane on each side of the tablet. The core of the tablet is composed of drug with small concentrations of excipients. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. When ingested, water is taken through the membrane, dissolving the drug, so it can then exit through the laser drilled ports in the membrane.

Table 4. Dosing and Administration with Metformin Extended-Release (Fortamet®)[10, 11]

Drug	Dosing
Fortamet® (metformin extended-release tablets) 500mg and 1000mg	Dosing should be individualized on the basis of effectiveness and tolerance, while not exceeding the maximum recommended daily dose. Maximum daily dose = 2,500mg Usual starting dose = 500-1,000mg QD (clinically significant responses are not seen at doses below 1500mg per day, however, lower doses can be used and increased gradually to minimize gastrointestinal symptoms.) Titration = Made in increments of 500mg weekly, up to the maximum daily dose. Metformin extended-release should be given QD with the evening meal. Initial dosing should be started low, with gradual dose escalation, to reduce and minimize gastrointestinal adverse events, and to identify the minimum dose required for adequate glycemic control. Studies of patients currently treated with immediate-release metformin and switched to metformin extended-release showed that patients may be safely switched to metformin extended-release QD at the same total daily dose. Glycemic control should be monitored following any switch in dose of formulation, and dosing adjustments made as necessary. When transitioning patients from other hypoglycemic agents to metformin extended-release, a transition period is generally not necessary. Special care should be given to patients transitioning from chlorpropamide during the first two weeks, as chlorpropamide can be retained, leading to overlapping drug effects and possible hypoglycemia. When patients have not responded to four weeks of the maximum dose of metformin extended-release, consideration should be given to the gradual addition of another anti-diabetic agent (sulfonylurea). In diabetic patients receiving insulin, metformin extended-release therapy should be initiated at 500mg QD, and increased in increments of 500mg Qweek until adequate glycemic control is achieved.

Special Dosing Considerations

Metformin extended-release is not recommended for use during pregnancy (Category B) and in patients below the age of 17 years.[10] No pediatric clinical studies have been conducted with Metformin extended-release, therefore; the safety and efficacy of extended release metformin formulations have not been established in pediatric patients.[13] The extended-release tablets should not be crushed or chewed.

VIII. Effectiveness

The management of diabetes combines diet, exercise, drug therapy, and management of co-morbidities. The type of patient being treated determines choice of a first-line agent. For obese patients, metformin is generally preferred, while in non-obese patients, a sulfonylurea or short acting secretogogue is preferred. Metformin is also preferred with early insulin resistance, and for the elderly, a sulfonylurea, short acting secretion promoting agent, alpha-glucosidase inhibitor, or insulin is recommended.[10] In terms of benefit from drug therapy, the closer to normal the better the results. It has been estimated that for every 1% point lowering of A1C, there is a 35% decrease in the risk of diabetic complications.

Metformin extended-release (Fortamet®) was approved for marketing on the basis of clinical and pharmacokinetic studies that compared once daily metformin extended-release (Fortamet®) to the innovator product, which in this case is Glucophage® (immediate-release metformin) given twice daily. Limited peer-reviewed, published clinical data is available. One pivotal study showed that QD metformin extended-release (Fortamet®) is clinically non-inferior to BID immediate-release metformin. Additionally, pharmacokinetic studies demonstrated the bioavailability of QD metformin extended-release as similar to that of BID immediate-release metformin. Table 5 describes clinical data available for metformin extended-release (Fortamet®), as included in the manufactuer's package insert. Data from the package insert on immediate-release metformin and insulin will not be described, as this review is focused on metformin extended-release. Additionally, any unpublished data or data presented in posters (abstract form) is not included in the review.

Table 5. Clinical Efficacy Studies for Metformin Extended-Release (Fortamet®)[10,13]

Study Design	Sample	Treatment and Duration	Results
Double-blind, randomized, active-controlled, multicenter study	n=680	Metformin extended-release (Fortamet®) QD vs. immediate-release metformin BID, for 20 weeks	In evaluating the change in HbA1C from baseline to endpoint, in order to demonstrate the clinical non-inferiority of metformin extended-release compared with immediate-release metformin: • Metformin extended-release and immediate-release metformin patients had mean HbA1C changes from baseline to endpoint equal to +0.40 and +0.14, respectively (a difference in mean change of 0.25%). The comparison of primary efficacy measures, mean change in A1C from baseline to endpoint, was deemed clinically non-inferior by virtue of the difference in mean change being <0.4%. • The least-square mean treatment difference was 0.25 (95% CI = 0.14, 0.37) demonstrating that metformin extended-release was clinically similar to immediate-release metformin. • Mean changes for fasting plasma glucose and plasma insulin were small for both metformin extended-release (change from baseline to endpoint 10mg/dL) and immediate-release metformin (4.2mg/dL), and were not clinically meaningful (p=0.032). • 22% and 14% of the metformin extended-release and immediate-release study patients, respectively, discontinued prematurely from the trial. • 5% of patients on metformin extended-release withdrew because of a stated lack of efficacy, as compared with 2% on immediate-release metformin (p=0.047). • Results from this study also suggested that neither metformin extended-release nor immediate-release metformin were associated with weight gain or increases in body mass index.

Additional Evidence

Dose Simplification: In a 24 week double-blind, randomized study of metformin XR once daily (1,000mg and 1,500mg QD), and metformin immediate-release given twice daily (500mg BID), patients were evaluated after eight weeks of pre-study treatment with metformin 500mg BID for eight weeks.[10] Table 6 displays the results. At 12 weeks, there was an **increase in HbA1c** in all groups, with the metformin XR 1,000mg group having a statistically significant increase of 0.23%.

Table 6. Metformin Immediate-Release vs. Metformin XR[10]

	Metformin 500mg BID	Metformin XR 1,000mg QD	Metformin XR 1,500mg QD
HgA1C	n=67	n=72	n=66
Baseline	7.06	6.99	7.02
Change at 12 weeks	0.14	**0.23**	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at final visit	0.14[a]	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dl)	n=69	n=72	n=70
Baseline	210.3	202.8	192.7
Change at 12 weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at final visit	0.9	**1.1**	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

[a]n=68

Another study looking at adherence indices for metformin and sulfonylureas in 2,920 patients showed that adequate adherence (= 90%) was found in 31% of the prescribed sulfonylureas alone and in 34% of those prescribed metformin alone.[14] There were significant trends of poorer adherence with each increase in the daily number of tablets taken (p=0.001) and increase in co-medication (p=0.0001) for sulfonylureas alone after adjustment for other factors. This study did not look at the long-term impact of adherence issues in this diabetic population.

Yet another study has evaluated adherence to oral antidiabetic agents.[15] This study evaluated medication adherence among patients receiving monotherapy with metformin or glyburide, combination therapy with metformin and glyburide, and fixed-dose combination therapy (glyburide/metformin). There were no significant differences in adherence rates among 6,502 newly treated patients receiving monotherapy, combination therapy, or fixed-dose combination therapy. Among 1,815 patients previously treated with glyburide or metformin monotherapy who required addition of another agent, resulting in combination therapy, adherence rates were significantly lower (54%) than in the 105 patients receiving monotherapy who were switched to fixed-dose combination therapy (77%). Similar results were observed in patients receiving combination therapy who were switched to fixed-dose combination therapy (71% vs. 87%; p<0.001).

In a multicenter, randomized, double-blind, parallel group study in patients with Type 2 diabetes, eligible patients were to have a HbA1C of 8.5% and a mean fasting plasma glucose concentration = 200mg/dl while receiving metformin immediate-release (MIR) 500mg BID for at least eight weeks.[16] After two weeks, patients were randomly assigned to receive a metformin extended-release (MXR) formulation at 1,000mg or 1,500mg QD for 24 weeks or continue on the current dose of immediate-release metformin. Two hundred seventeen patients were randomized to treatment. The mean change from baseline in HbA1c values at weeks 12 and 24 were small and similar in the three treatment groups. At week 12, the mean change from baseline in HbA1c was 0.15% for MIR, 0.23% for MXR 1,000 mg, and 0.04% for MXR 1,500 mg. The corresponding mean changes at week 24 were 0.06%, 0.25%, and 0.14%. Patients previously on MIR achieved comparable

glycemic control when therapy was switched to once-daily MXR at the same or greater total daily dose. (Note: The MXR formulation in this review was not identified as Fortamet®.)

Stable Therapy: When transferring from sulfonylurea agents to metformin, a transition period generally is not required, and the sulfonylurea agents may be abruptly discontinued.[11] Close monitoring is necessary during this transition period.

In a randomized trial, patients currently treated with metformin immediate-release were switched to metformin XR.[10] Results of the study showed patients receiving metformin treatment may safely be switched to metformin XR once daily at the same total daily dose, up to 2000mg given once daily.

Impact on Physician Visits: No data from studies relating to physician visits or use of medical services with metformin (metformin and metformin XR) is available through manufacturer literature databases. A literature search using Medline/Pubmed and Ovid produced limited peer-reviewed data relating to utilization of medical resources with metformin. The data that was pulled was from pharmacoeconomic studies, and evaluated overall costs of treatment for the first-line treatments in diabetes. Because cost information is not a consideration in reviews for the PDL, this data has not been included.

IX. Conclusions

One pivotal clinical study shows metformin extended-release efficacy for diabetes is non-inferior to immediate-release metformin. No direct comparative studies have evaluated the efficacy of Fortamet® with Glucophage® XR. Additional clinical data is lacking due to Fortamet®'s approval based on clinical and pharmacokinetic studies comparing Fortamet® and immediate-release metformin. Although metformin extended-release offers once daily dosing and a smaller tablet size, these factors alone have not been shown to result in improved efficacy of this product over other metformin formulations.

Fortamet® is approved for similar indications as immediate-release metformin, and is the first metformin extended-release product available in a 1,000mg dosage form. Although this product is a once-daily agent, multiple studies have suggested this does not have a significant impact on the endpoint of the disease (HbA1c) when compared to immediate-release metformin given twice daily.

Looking at availability, a generic formulation is available for immediate-release metformin (Glucophage®) 500mg, 850mg, and 1,000mg tablets, and for extended-release metformin (Glucophage® XR) 500mg tablets. Fortamet® is available brand only, as a 500mg and 1,000mg tablet.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand of metformin extended-release (Fortamet®) is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review-
EstroGel 0.06% (Estradiol Gel)
Estrogens, AHFS Class 681604
January 26, 2005

I. Overview

Estrogens are derived from naturally occurring hormones. Science has since formulated synthetic steroidal and non-steroidal compounds with estrogenic activity. The estrogens in the body are regulated by a complex feedback cycle that results in ovulation and menstruation, and at menopause, estrogen production declines. The average age of onset of menopause is estimated to be 51.4 years; however, earlier loss of ovarian function may occur secondary to ovarian surgery, endocrinologic and autoimmune disorders, and smoking.[1]

Decreased estrogen levels may trigger alterations in the body that result in genitourinary atrophy, vasomotor instability, blood lipid alterations, cardiovascular diseases, insomnia, psychosexual disorders and osteoporosis, thus having an effect on quality of life. Estrogen replacement therapy (ERT) and estrogen plus progestin therapy (HRT) are important to women's health. Because estrogen receptors are located in multiple areas of the body, estrogen has been shown to have additional health benefits beyond vasomotor symptom management, as well as potential risks. As a result of the July 2002 findings from the estrogen / progestin arm of the Women's Health Initiative (WHI) trial, the Food and Drug Administration (FDA) has updated label warnings on all estrogen products, and several professional organizations have recommended against use of estrogen and combination products for the prevention of chronic conditions. In 1999, estrogens were the number one prescribed drug class for women aged 45-64.[2]

Data places the number of women in the United States over the age of 50 years, at 50 million.[1] Given the current life expectancies, women can expect to live one-third of their life span after the onset of menopause. In 2002, national Medicaid use of estrogens resulted in 102 prescriptions per 1,000 members.[3] Various estrogen formulations are available. Transdermal, intramuscular and topical estrogen treatments are alternatives with differing hormonal compositions and consequences of first-pass metabolism.

The estrogen class was originally reviewed in March 2004. The original review of the estrogen products is available in full for reference in Appendix A. This review encompasses all dosage forms and strengths.

II. Current Treatment Guidelines

In postmenopausal women, estrogens are effective for treating vasomotor symptoms, vaginal atrophy and they also help prevent bone loss associated with osteoporosis. However, with the introduction of the 2002 Women's Health Initiative (WHI) results and growing use of evidence-based medicine, many medical organizations now suggest that **ERT / HRT be used only for management of vasomotor symptoms, using the lowest dose for the shortest duration**. While estradiol gel was not included in the WHI trial, in the absence of conclusive data, a conservative view would assume the risks to be similar to oral estrogens. Because of the risks of endometrial cancer, very close monitoring of all women taking estrogens is important. Topical vaginal products should especially be considered when ERT / HRT is only being considered for the treatment of vaginal atrophy. In addition, labeling for oral estrogen agents has been updated to reflect the following changes:[4]

- Other non-estrogen therapies should be carefully considered if ERT / HRT is being used for the sole purpose of osteoporosis prevention.
- Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

A number of recent studies, including the WHI trial, have played an important role in the current treatment recommendations for ERT / HRT in postmenopausal women. Treatment with ERT / HRT, now more than ever, is a decision to be made on an individual basis. The following are significant findings from several studies.

Women's Health Initiative (WHI)[5-15]

The Women's Health Initiative 15-year, three-part, research program of 162,000 American women, was established to address the common causes of death, disability and poor quality of life in postmenopausal women. The program documented findings on cardiovascular disease, cancer and osteoporosis. In July 2002, researchers stopped the estrogen plus progestin arm of the study after the findings suggested the associated health risks outweighed the benefits, and concluded combined estrogen and progestin therapy is not suitable for the prevention of chronic diseases. Researchers are continuing to report data from other arms of the study (Premarin only) and final results will be released in 2005. The following outcomes from the estrogen plus progestin (Prempro) study (n=16,608) have been influential in the treatment of postmenopausal women:

- 24% reduction in all fractures and a 33% reduction in hip fractures.
- Increase in hipbone density 3.7% after 3 years of treatment compared to 0.14% for placebo.
- 19% decrease in endometrial cancer and 58% increase in ovarian cancer rates.
- 24% overall increase in the risk of coronary heart disease.
- 81% increased risk of heart disease in the first year after starting treatment.
- 24% increase risk for breast cancer due to treatment.
- For every 10,000 women followed for 1 year, one would expect to see 31 strokes in women on estrogen plus progestin compared to 24 with placebo. (31% increase in the risk for stroke).
- There were no clear benefits in the estrogen plus progestin study group on any of the quality of life measures.

Hormonal replacement after breast cancer-is it safe? A randomized comparison: HABITS trial stopped.[16]

A safety analysis study, one of two studies started to evaluate hormone replacement therapy safety in 345 women with previous breast cancer, was stopped early, as reported in the February 2004 issue of *The Lancet*. Women were randomized to 2 years of hormone replacement therapy or best symptomatic treatment without hormones (no HRT). The primary endpoint was any new breast cancer event. Early findings showed that 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. The trial was stopped when these findings were discovered and determined to be an unacceptable risk for women exposed to HRT.

Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women (Well-HART Trial)[17]

The Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial was a double-blind, placebo-controlled trial of 225 postmenopausal women, who were randomized to usual care with estrogen or estrogen plus progestin (medroxyprogesterone). Women were included if they were 75 years of age or younger, had LDL levels of 100-250mg per deciliter, triglyceride levels of less than 400mg per deciliter, and had at least one coronary-artery lesion occluding 30% or more of the luminal diameter. Primary outcome measure was the average per-participant change between baseline and follow-up coronary angiograms in the percent stenosis measured by quantitative coronary angiography. The mean change in the percent stenosis was 1.89 ± 0.78 percentage points in the control group, 2.18 ± 0.76 in the estrogen group, and 1.24 ± 0.80 in the estrogen plus progestin group. These results showed that estrogen or estrogen plus progestin has no significant effect on the progression of atherosclerosis in postmenopausal women.

Heart, Estrogen/Progestin Replacement Study[18]

The Heart, Estrogen/Progestin Replacement Study (HERS) was the first large randomized, placebo-controlled clinical trial that looked at the effect of HRT on women with heart disease. The study involved 2,763 women average age 67, who were treated with HRT for 4 years. The results of the study showed that HRT did not prevent further heart attacks or death from coronary heart disease in women with pre-existing heart disease. This outcome occurred despite an 11% reduction in LDL cholesterol and an increase by 10% in HDL cholesterol levels. Increased risk of deep venous thrombosis and pulmonary embolism was also documented with HRT. Investigators concluded women with heart disease should not be started on HRT to prevent heart attacks until data from on-going trials is available.

Postmenopausal Estrogen/Progestin Interventions Trial[19]

The Postmenopausal Estrogen / Progestin Interventions Trial (PEPI), sponsored by the National Heart, Lung, and Blood Institute and other units of the National Institutes of Health, was conducted over 3 years and involved 875 women, ages 45-64. PEPI tested four hormone regimens: estrogen alone, taken daily; estrogen taken daily with medroxyprogesterone, for 12 days a month; estrogen plus medroxyprogesterone taken daily; and estrogen taken daily plus micronized progesterone, for 12 days a month. The study evaluated ERT / HRT and heart disease risk factors, but was not large or long enough to fully evaluate the long-term effects. The key findings were that each of the hormone therapies improved key heart disease risk factors: increase in HDL and a decrease in LDL and fibrinogen. The study also showed slowed bone loss and significant increase in bone mass.

Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. [20]

This study reports the endometrial results from patients enrolled in a subset of the Women's HOPE (Health and Osteoporosis, Progestin and Estrogen) Study. The study looked at the endometrial safety of 2 years of lower doses of continuous combined estrogen and medroxyprogesterone. Eight hundred and twenty-two study participants were taken from 19 centers across the United States, and were randomized to estrogen alone, estrogen plus progestin or placebo. Results showed that two years of treatment with lower doses of the estrogen plus progestin combination provided endometrial protection comparable to that seen with commonly prescribed dosages. Risk of endometrial hyperplasia in patients who took estrogen alone, was shown to increase with dose and duration.

Treatment Guidelines and Recommendations

U.S. Preventative Services Task Force 2002[21]
1. The U.S. Preventative Services Task Force has recommended against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. The committee did not evaluate the use of HRT to treat vasomotor or urogenital symptoms, but recommend the benefits and harms of treatment be balanced with individual preferences, risks for chronic diseases, and presence of menopausal symptoms.
2. There is insufficient evidence to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

American Association of Clinical Endocrinologists[22]
8. Menopausal hormone therapy must be individualized taking into consideration the benefits, risks, and alternatives. It is essential for a woman contemplating menopausal hormone therapy to discuss these issues with her physician.
9. Menopausal therapy is appropriate for women with moderate to severe vasomotor symptoms associated with estrogen deficiency, quality of life symptoms resulting from estrogen deficiency, and significant symptoms related to vaginal atrophy.
10. Strong consideration should be given to alternative pharmacologic therapy options for prevention and treatment of osteoporosis in patients not electing to take menopausal hormone therapy.
11. Menopausal therapy is not indicated solely for the primary or secondary prevention of cardiovascular disease.
12. Hormone therapy should be at the minimum dose that improves symptoms and used for only so long as symptoms remain significant when assessed intermittently off of therapy.

The North American Menopause Society[23]
1. Progestin should be added to estrogen therapy in all postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. All U.S. FDA approved progestin formulations will provide endometrial protection if the dose and duration are adequate. Evidence is lacking to recommend topical progesterone for preventing estrogen-induced endometrial hyperplasia.

Institute For Clinical Systems Improvement[24]
1. ICSI guidelines focus on the management of symptoms and conditions commonly associated with menopause, with emphasis on the role of hormone therapy relative to other available options. Although hormone therapy is often the most effective treatment for menopausal symptoms, it is not always necessary. 2. Women using hormone therapy must be regularly evaluated regarding their continued requirements for treatment, especially if there has been any change in their overall health status. 3. Women who have recently discontinued hormone therapy are at risk for rapid bone loss and must be identified and monitored to ensure continued bone health. 4. The role of hormone replacement therapy in disease prevention has been all but eliminated in current practice. 5. The exact risks with hormone therapy, as well as side effects, may not be fully defined, but they cannot be dismissed and must always be considered and discussed as part of the collaborative decision-making process. 6. Careful consideration and in-depth discussion are required for the initiation or continuation of hormone therapy, based on individual values and priorities, as well as risks and benefit.

Food and Drug Administration[25]
1. Hormones should not be taken for cardiovascular protection. 2. If ERT / HRT is being used for osteoporosis prevention, consideration should be given to taking other alternative treatments that have not been shown to increase the risk of breast cancer. 3. Women looking to discontinue treatment who have had success in treating vasomotor symptoms, should do so slowly over time-possibly as long as 6 months. 4. All women taking ERT / HRT should speak to their physicians about the risks and benefits of continuing treatment. 5. In late February 2004, the FDA also asked manufacturers of hormone replacement therapies to add a warning to their labels-that hormone replacement may increase older women's risk of Alzheimer's disease or other types of dementia, another change from what was previously believed.

III. Indications

Estradiol 0.06% gel (EstroGel®) provides systemic estrogen replacement by releasing estradiol, which is the major estrogenic hormone secreted by the human ovary. Estradiol gel is specifically indicated for the following uses[26]:

1) Treatment of moderate to severe vasomotor symptoms associated with menopause.
2) Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

Estrogens, including estradiol gel, are contraindicated with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism, or history of either condition.
- Active or recent arterial thromboembolic disease.
- Liver dysfunction or disease.
- Known hypersensitivity to ingredients in estradiol 0.06% gel.

IV. Pharmacokinetics

Percutaneous use of estradiol gel produces plasma concentrations of estradiol and estrone similar to that observed in the follicular phase of the ovulatory cycle[26]. Therapeutic levels for relief of vasomotor symptoms range from 40-80pg/mL.

Absorption
Active ingredient from the estradiol gel product is absorbed by a passive diffusion process via transport across the skin.[27] The rate of diffusion across the stratum corneum is the rate limiting factor. When estradiol gel is applied directly to skin, it dries within 2-5 minutes.

In a study of 24 postmenopausal women, estradiol gel was applied once daily on the posterior surface of one arm from the wrist area to the shoulder for 14 days.[27] Mean serum concentrations of estradiol and estrone on day 14 were 46.4pg/ml and 64.2pg/ml, respectively. The time-averaged serum estradiol and estrone concentration over the 24-hour dose interval after administration of 1.25g estradiol gel on day 14 are 28.3pg/mL and 48.6pg/ml. In a separate analysis of 23 postmenopausal women who received 2.5g estradiol gel once daily for 11 days, the serum concentrations of estradiol appeared to reach steady state after the third daily application.

Distribution
The distribution pattern of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

Metabolism and Excretion
Metabolism of estrogens is similar between exogenous estrogens and endogenous estrogens.[27] Metabolism is primarily hepatic. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is predominately excreted in urine. Estrogens, including estradiol, also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, circulating estrogens exist as sulfate conjugates and serve as a circulating reservoir for the formation of more active estrogens. Estradiol absorbed from EstroGel® does not undergo first pass hepatic metabolism.

Estradiol, estrone, and estriol are primarily excreted in the urine alone with glucuronide and sulfate conjugates. The apparent terminal exponential half-life for estradiol was about 36 hours following administration of estradiol gel 1.25g.[26, 27]

V. Drug Interactions

Drug interactions have not been assessed for estradiol gel (EstroGel®).[26, 27, 28]

In vitro and in vivo studies have suggested that estrogens are metabolized partially by cytochrome P450 3A4. As a result, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 include St. John's Wort, phenobarbital, carbamazepine, and rifampin. These drugs may result in a decrease in the therapeutic effects of estrogens and may cause uterine bleeding. Inhibitors of CYP3A4 include erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice. Inhibitors can result in increased plasma concentrations of estrogens and side effects.

Table 1 further defines the Level 1 and Level 2 drug interactions.

Table 1. Significant Drug Interactions with Estrogens[28]

Significance	Interaction	Mechanism
Level 2 Delayed, moderate, suspected	Estrogens (including estradiol) and Barbiturates	Induction of hepatic microsomal enzymes by barbiturates increases elimination of estrogens, decreasing the plasma concentration.
Level 2 Delayed, moderate, suspected	Estrogens (including estradiol) and Corticosteroids	Inactivation of hepatic cytochrome p450, which may result in decreased formation of the 6-betahydroxy metabolite of prednisolone, resulting in an increase in the pharmacologic and toxic effects of corticosteroids.
Level 2 Delayed, moderate, suspected	Estrogens (including estradiol) and Hydantoins	Induction of hepatic microsomal enzymes leading to increased metabolism of estrogens has been suggested. Protein binding of phenytoin may be affected. Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. Loss of seizure control has been suggested, but not confirmed.
Level 2 Delayed, moderate, suspected	Estrogens (ethinyl estradiol) and Modafinil	Induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of ethinyl estradiol by modafinil is suspected, causing the efficacy of estrogens to be impaired.
Level 2 Delayed, moderate, suspected	Estrogens (including estradiol) and Rifamycins	Rifamycins induce drug metabolizing enzymes of estrogens in the liver. Metabolism is increased 4-fold in vitro and in vivo. AUC and half-life also are decreased. The effect is impairment of estrogens; menstrual disturbances have been noted.
Level 2 Delayed, moderate, probable	Thyroid hormone and estrogens (including estradiol)	Changes in serum thyroxine and thyrotropin concentrations induced by estrogen administration may result from the increase serum thyroxine-binding globulin concentrations in hypothyroid women. Serum free thyroxine concentration may be decreased, increasing serum thyrotropin concentration and increasing the need for thyroid hormone.
Level 2 Delayed, moderate, suspected	Estrogens (including estradiol) and Topiramate	Topiramate may increase the metabolism of estrogens resulting in decreased efficacy of estrogens.

VI. Adverse Drug Events

Black Box Warning[26]

Estrogens Increase the Risk of Endometrial Cancer
Close surveillance of all women taking estrogen is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent doses.

Cardiovascular and Other Risks
Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo.

Other does of conjugated estrogens with medroxyprogesterone and other combinations and dosage forms of estrogens and progestins were not studies in WHI clinical trials, and in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Effect of Washing the Application Site
In a study of 24 postmenopausal women who applied 1.25g of estradiol gel once daily for 14 days, site washing one hour after the application resulted in a 22% mean decrease in average 24-hour serum concentrations of estradiol.[27]

Estradiol gel (EstroGel®) 1.25g was studied in two well-controlled 12-week clinical trials. The incidence of adverse experiences = 5% for 1.25g estradiol gel and placebo are described in Table 2.

Table 2. Adverse Events (Incidence = 5%) with Estradiol Gel (EstroGel®) and Placebo[26]

Adverse Reaction By Body System	EstroGel 1.25g/day (n=168)	Placebo (n=73)
Body as a Whole		
Headache	20.2	17.8
Infection[a]	17.3	6.8
Pain[b]	7.1	11.0
Abdominal Pain	7.7	1.4
Back Pain	4.8	4.1
Flu Syndrome	5.4	1.4
Asthenia	4.8	4.1
Cardiovascular System		
Palpitations	0.6	1.4
Digestive System		
Nausea	6.0	4.1
Flatulence	6.5	5.5
Diarrhea	4.2	0.0
Metabolic and Nutritional		
Weight Gain	2.4	0.0
Nervous System		
Nervousness	2.4	1.4
Depression	3.0	2.7
Anxiety	1.8	0.0
Respiratory System		
Sinusitis	3.6	1.4
Rhinitis	2.4	6.8
Skin and Appendages		
Rash[c]	7.1	5.5
Pruritus[c]	4.8	2.7
Application Site Reaction	0.6	0.0
Urogenital		
Breast Pain	12.5	9.6
Metrorrhagia	3.0	0.0
Endometrial Disorder[d]	1.8	1.4
Vaginitis	8.9	4.1
Pap Smear Suspicious[e]	5.4	2.7
Vaginal Hemorrhage	1.2	0.0

a Infection: Upper respiratory infection, common cold, eye infection.
b Pain: Generalized and extremity aches/pains, cramps.
c Rash and Pruritus: More than half of the EstroGel treated patients who had pruritus reported itching at a body site other than the arms or reported generalized itching or itching skin. Similarly, most of the EstroGel treated patients with rash had rash on one or more areas of the body in addition to the arms.
d Endometrial Disorder: Proliferative endometrium, benign endometrial disorders.
e Pap Smear Suspicious: Atypical squamous cells of undetermined significance, inflammatory changes, epithelial cell abnormality.

Other Reported Adverse Events[26]:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; dysmenorrheal; increase size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: Tenderness; enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes, breast cancer.

Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: Nausea; bloating; diarrhea; dyspepsia; constipation; vomiting; abdominal cramps; cholestatic jaundice; increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas.

Skin: Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme, erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes: Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System: Headache; migraine, dizziness; mental depression; chorea; nervousness; mood disturbances; irritability exacerbation of epilepsy.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbations of asthma; increased triglycerides.

VII. Dosing and Administration

Use of estrogen, alone and in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for each individual women. Women should be monitored and re-evaluated at 3 to 6 month intervals to determine if treatment is still necessary. When estradiol gel is prescribed for postmenopausal women with a uterus, a progestin should be initiated to reduce the risk of endometrial cancer. Women with an intact uterus should undergo diagnostic measures, such as endometrial sampling, when indicated, to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Table 3. Dosing and Administration with Estradiol Gel (EstroGel®)[26, 27, 29]

Drug	Dosing
Estradiol gel 0.06% (EstroGel®) Delivers 1.25g of gel containing 0.75mg of estradiol per pump depression Available in 80g tube and 93g pump	Estradiol gel contains 0.06% 17B-estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. The gel should be applied over a large area (approximately 2000cm^2) of the skin in a thin layer. The recommended area of application is the arm, from wrist to shoulder. The gel should not be applied to the breast. Do not allow others to apply the gel. Apply topical estradiol gel at the same time each day. Apply daily dose of gel to clean, dry, unbroken skin. Apply topical estradiol gel dose after bath, shower, or sauna. Try to leave as much time as possible between applying topical estradiol gel dose and going swimming. Be sure skin is completely dry before applying topical estradiol gel. Note: This gel is an alcohol-based product, avoid fire, flame, and smoking until the gel has dried.

	Pump: Before using the pump for the first time, it must be primed. Remove the large pump cover and fully depress the pump twice. Discard the unused gel by thoroughly rinsing down the sink or placing it in the household trash in a manner that avoids accidental exposure or ingestion by household members or pets. After priming, the pump is ready to use; 1 complete pump depression will dispense the same amount of topical estradiol gel each time. The topical estradiol gel pump contains enough product to allow for initial priming of the pump twice and to deliver 64 daily doses. After the pump has been initially primed twice and 64 doses have been dispensed, discard the pump. To apply the dose, collect the gel into the palm of the hand by pressing the pump firmly and fully with 1 fluid motion without hesitation. Apply the gel to one arm using the hand. Spread the gel as thinly as possible over the entire area on the inside and outside of the arm from wrist to shoulder. Always place the cap back on the tip of the pump and the large pump cover over the top of the pump after each use. Wash hands with soap and water after applying the gel to reduce the chance that the medicine will spread to other people. It is not necessary to massage or rub in topical estradiol gel. Simply allow the gel to dry for up to 5 minutes before dressing. **Tube:** When using the topical estradiol tube, gently squeeze topical estradiol gel from the tube to fill the applicator to the halfway mark (1.25 mark). Apply the gel to one arm using the applicator. Be sure to transfer all of the gel from the applicator to the arm.

Special Dosing Considerations
Estradiol gel should not be used during pregnancy (Pregnancy Category X).[26, 27] The drug is also not indicated for use in children. There have been insufficient numbers of geriatric patients involved in studies utilizing estradiol gel, to determine whether those over 65 years of age differ from younger subjects in their response to the gel.

VIII. Effectiveness

Published, peer reviewed efficacy data is reported in Table 4.

Table 4. Clinical Efficacy Studies for Estradiol Gel (EstroGel®)

Study Design	Sample	Treatment and Duration	Results
Randomized tolerability study of 17B-estradiol vs. placebo[30]	n=221	17B-estradiol gel 1.25g or 2.5g*, or placebo gel *Dose not approved in the U.S.	To determine the efficacy and tolerability of two strengths of estradiol gel in controlling vasomotor symptoms of menopause: • A significant reduction ($p<0.05$) in the mean frequency of moderate to severe hot flashes and mean frequency and severity of all hot flashes was observed with both estradiol gel groups compared with placebo. • The mean number of moderate to severe hot flashes at the end of he study with the estradiol gel 2.5g, estradiol gel 1.25g, and placebo gel was 2.0 (±4.2), 2.8(±3.7), and 5.2 (±6.5), respectively. • Adverse events were not significantly different among groups, however, a higher incidence of estrogen-related adverse events was reported with the estradiol gel 2.5g dose.
Open-label, randomized, parallel group study[31] *Oestrogel® (oestradiol gel) is a registered product from France-dose is not approved in the U.S.	n=63	Group I: Oestrogel® 2.5g* days 1-25 Group II: Conjugated estrogens 0.625mg days 1-25 Group III: Oestrogel® 2.5g days 1-25 + micronized progesterone 200mg days 12-25 Group IV: Conjugated estrogens 0.625mg days 1-25 + micronized progesterone 200mg days 12-15	To compare the endocrinological and clinical effects of percutaneous estradiol and oral conjugated estrogens as replacement therapy in menopausal women: • No difference was found between any of the four groups with regard to reduction in hot flashes, and insomnia/night sweats at any time point in the study. • No difference was found between each treatment group with regards to improvements in vaginal atrophy at any time point.
Multicenter, double-blind, parallel, placebo controlled study[32]	n=39	Estradiol gel 2.5g* vs. placebo *2.5g dose is not approved in the U.S.	In evaluating the safety and efficacy of estradiol gel in the treatment of menopausal symptoms: • Severity of hot flashes was significantly reduced in the estradiol gel group compared with placebo. • Frequency of hot flashes was reduced significantly at every week of therapy versus placebo ($p<0.01$). • Vaginal atrophy occurred in 29% of the placebo group versus none in the estradiol gel group ($p<0.01$). • Adverse events were mild except for breast tenderness, and the frequency and type of adverse events were similar between groups.
Randomized,	n=254	6 month study of estradiol	To compare the impact of percutaneous oestradiol gels in

open-label, multicenter study[33] *Estreva® (oestradiol gel) is a registered product from Monaco-dose is not approved in the U.S.		gel (Oestrogel®) 1.5mg/day, day 1-24 + nomegestrol acetate 5mg, days 11-24 or Estradiol gel (*Estreva®) + nomegestrol acetate 5mg, days 11-24	postmenopausal women, on clinical symptoms and endometrium: • Climacteric symptoms rapidly relieved with both treatments and no statistical difference between treatment groups was noted. • Vaginal atrophy decreased significantly from a baseline of 40% before treatment to 8% after 6 months of therapy. No differences between treatment groups was found.
Randomized, parallel group, controlled, open-label study[34]	n=120	12 month study comparing estradiol gel (*Divigel®/*Sandrena®) 1g/day + dydrogesterone 10mg/day, days 1-12 or Estradiol patch 50mcg/day (Estraderm TTS®) + dydrogesterone 10mg/day, days 1-12 *Dose not approved in the U.S.	In evaluating transdermal oestrogen therapy in postmenopausal women, comparing estradiol gel and estradiol patch: • Menopausal symptoms were reduced in both treatment groups significantly by week 2 of the study ($p<0.001$ for hot flashes, sweating, dry vagina, and insomnia; $p<0.05$ for depressive mood). • Acceptability of treatment was higher in the gel group (96.4%) than in the patch group (90.7%). • Adverse events were reported in 3.3% (skin irritation) of the estradiol gel group and in 46.7% in the patch group ($p<0.001$). • Ten patients in the gel group and eight in the patch group reported adverse events. The most frequently reported adverse event was headache and breast tension.
Randomized, open-label study[35]	n=173	Two year study of… 1) Estradiol gel (*Divigel®/*Sandrena®) 1g/day for 3 months + medroxyprogesterone 20mg/day the last 14 days 2) Estradiol gel (*Divigel®/*Sandrena®) 2g/day for 21 days + medroxyprogesterone 10mg, last 14 days 3) Oral estradiol 2mg/day for 3 weeks + medroxyprogesterone 10mg, last 10 days *Dose not approved in the U.S.	When comparing transdermal oestradiol gel with oral therapy in the treatment of climacterium: • Menopausal symptoms (not flashes, sweats, anxiety, insomnia, depressive symptoms, dizziness, loss of libido, vaginal dryness, and headaches) were reduced in all 3 treatment groups to a significant extend by 1 month of therapy and symptoms continued to decline throughout the study. • Adverse events were not significantly different between groups and included breast tension, unspecific cardiac symptoms, fatigue, headache, and depressive symptoms. • The gel product was well tolerated with little skin irritation reported (<3% for both years).
Six month study of progestin addition to estradiol gel therapy[36]	n=22	Estradiol gel 5g/day* alone or Estradiol gel 5g/day* + Lynestrenol 5mg on days 11-21	When a progestin was added to estradiol gel therapy, the effects on vasomotor symptoms and mood were: • A reduction in hot flashes and sweats were not significantly different in the first month of treatment, however, were significantly lower in the estradiol/progestin group in months 2-6, as compared with the estrogen only group ($p<0.0005$). • Negative mood symptoms (tension, fatigue,

		*Dose not approved in the U.S.	irritability, and depression) were more pronounced in the estrogen/progestin group than in the estrogen only group.
Two year double-blind, placebo controlled study[37]	n=110	Estradiol gel 5g* days 1-24 + oral micronized progesterone 200mg, days 13-24 or Topical placebo or oral estradiol 2mg day 1-21 + oral cyproterone 1mg days 12-21 or Oral placebo *Dose not approved in the U.S.	In analyzing climacteric symptoms after oral and percutaneous hormone replacement therapy: • Mean symptom scores were rapidly and similarly reduced in both active treatment groups ($p<0.001$), and remained low throughout the study. • Serum estrone to estradiol concentration ratios were 1 in the transdermal group but were >5 in the oral estradiol group.

Additional Evidence

Dose Simplification: No clinical studies with estradiol gel have evaluated the effect on compliance, with the once-daily treatment. One study presented above showed that acceptability with estradiol gel was greater as compared with a transdermal patch.[34]

One study looked at adherence with contraceptives, comparing adherence with the patch versus oral therapy. A study by Siseles, et al evaluated once (group B) and twice weekly (group A) transdermal estradiol delivery systems. [38] Blood samples were taken at the end of the wearing period: the 3rd day for Group A and the 7th day for Group B, to determine levels of estradiol, estrone, non-sex hormone binding globulin (SHBG)-bound estradiol and SHBG. Both treatments had similar clinical efficacy and were well tolerated. Plasma estradiol levels were higher in Group A throughout the study, probably owing to the different sampling times. SHBGand non-SHBG-bound estradiol were unchanged in both groups. There was a similar performance of both delivery systems. No further studies were found in Medline or Ovid that looked at compliance between once weekly and twice weekly hormone replacement patches.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical data on changing from one estrogen product to another, or from an oral agent to transdermal/percutaneous therapy.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical data pertinent to use of transdermal/percutaneous estrogens and physician visits.

IX. Conclusions

Estradiol gel 0.06% (EstroGel®) has been shown to be effective in treating menopausal symptoms, and is clinically comparable to other estrogen replacement delivery formulations (e.g., transdermal and oral). Estradiol gel is the first product available for percutaneous application, an additional route of administration for estrogen replacement. Estradiol gel is available in a pump or a tube. In addition to comparable clinical efficacy, the kinetics, drug interactions, and adverse events are similar for estrogens, in general use, regardless of the route of administration.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand of estradiol gel (EstroGel®) is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review-
Vytorin (Ezetimibe/Simvastatin)
Misc. Antilipemic Agents, AHFS Class 240692
January 26, 2005

I. Overview

Vytorin® is a combination of two drugs: simvastatin, a selective, competitive inhibitor of HMG-CoA reductase (statin, cholesterol-lowering agent); and ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption (misc. cholesterol-lowering agent).[1]

Simvastatin, which is also available as the brand product Zocor®, inhibits HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy -3-methylglutary-coenzyme A to mevalonate, a precursor of sterols (including cholesterol).

Ezetimibe is also available as the brand product Zetia®. Ezetimibe reduces blood levels of cholesterol by inhibiting the absorption of cholesterol by the small intestine. The drug localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe's mechanism of action is complementary to that of the HMG-CoA reductase inhibitors.

Hyperlipidemia is a major risk factor for the development of coronary heart disease (CHD).[2,3] Therefore, appropriate cholesterol and blood pressure control is essential to reduce the risk of morbidity and mortality associated with CHD. Ezetimibe/simvastatin (Vytorin®) is the first combination product combining both a cholesterol-lowering agent (statin) with an antihyperlipidemic agent that inhibits the absorption of cholesterol by the small intestine. Neither simvastatin nor ezetimibe are available generically.[4, 5]

Simvastatin/ezetimibe is available in various combination strengths.[1] This review encompasses all simvastatin/ezetimibe dosage forms and strengths. The previous Misc. Antilipemic Agents (AHFS 240692) pharmacotherapy review in full is available for reference in Appendix A.

II. Current Treatment Guidelines

Hyperlipidemia[2,3]

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) has issued recommendations for cholesterol management. According to the ATP III guidelines, therapy with lipid-altering agents is one of several components of multiple-risk-factor intervention in individuals at increased risk for CHD due to hypercholesterolemia. Therapeutic lifestyle changes (TLC) and drug therapy are the two major treatment modalities. The TLC Diet stresses reductions in saturated fat and cholesterol intake. The following table defines LDL-C goals and cutpoints for initiation of TLC and drug consideration based on the updated ATP III guidelines,[3] issued July 13, 2004. These updates advise physicians to consider new, more intensive treatment options for people at high and moderately high risk for a heat attack. The new guidelines are endorsed by the National Heart, Lung, and Blood Institute (NHLBI), the American College of Cardiology, and the American Heart Association.

Table 1. LDL-C Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories Based on Updated ATP III Guidelines[3]

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
High-Risk: CHD or CHD Risk Equivalents* (10-year risk >20%)	< 100 (Optional goal <70)‡	= 100¦	= 100†† (<100 consider drug options)**
Moderately-High Risk: 2+ Risk Factors† (10-year risk 10-20%)	< 130§	= 130¦	= 130 (100-129, consider drug options)‡‡
Moderate-Risk: 2+ Risk Factors† (10-year risk <10%)	< 130	= 130	= 160
Lower Risk: 0-1 Risk Factor†	< 160	= 160	= 190 (160-189, drug therapy optional)

†CHD risk equivalents include peripheral artery disease, abdominal aortic aneurysm and carotid artery disease, diabetes, and 2+ Risk Factors with a 10-year risk assessment greater than >20%. Diabetes qualifies as a CHD risk equivalent because it confers a high risk of new CHD within 10 years.

†Cigarette smoking, hypertension, low HDL-C (<40mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

‡Very high risk favors the optional LDL-C goal of <70mg/dL, and in patients with high triglycerides, non-HDL-C <100mg/dL.

§Optional LDL-C goal <100mg/dL.

¦ Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100mg/dL is a therapeutic option on the basis of available clinical trial results.

Major recommendations in the update include:

OVERVIEW:

- For high-risk patients, the overall goal remains an LDL-C level of <100mg/dL. For patients at very high risk (a subset of the high-risk category), the guidelines offer a new therapeutic option of treating to <70mg/dL. For very high-risk patients whose LDL-C levels are already <100mg/dL, there is an option to use drug therapy to reach the <70mg/dL goal.

CLASSIFICATION OF PATIENTS:

- **Lower/moderate-risk** patients are those with two or more risk factors plus an under 10% risk of a heart attack in ten years, or those with 0 to 1 risk factor.
- **Moderately high-risk** patients are those who have multiple (two or more) risk factors for CHD together with a 10% to 20% risk of heart attack within ten years.
- **High-risk** patients are those who have CHD or disease of the blood vessels to the brain or extremities, or diabetes, or multiple (two or more) risk factors (e.g., smoking, hypertension) that give them a greater than 20% chance of having a heart attack within ten years.
- **Very high-risk** patients are those who have cardiovascular disease together with either multiple risk factors (especially diabetes), or severe and poorly controlled risk factors or metabolic syndrome. Patients hospitalized for acute coronary syndromes, such as heart attack, are also at very high risk.

NEW GOALS:

- For high-risk patients, the update lowers the threshold for drug therapy to an LDL-C of 100mg/dL or higher and recommends drug therapy for those high-risk patients whose LDL-C is 100 to 129mg/dL. Previously this threshold for drug therapy was an LDL-C of 130mg/dL, and made drug treatment optional for LDL-C of 100 to 129mg/dL.

- For moderately high-risk patients, the goal remains an LDL-C <130mg/dL, but the update provides a therapeutic option to set a lower LDL-C goal of <100mg/dL and use drug therapy at LDL-C levels of 100-129mg/dL to reach this lower goal.
- The update does not revise recommendations for lower risk persons.
- The update advises that the intensity of LDL-lowering drug therapy be sufficient to achieve at least a 30% -40% reduction in LDL-C levels, through statins or combination therapy.

III. Indications

Simvastatin/ezetimibe is indicated for primary hypercholesterolemia and homozygous familial hypercholesterolemia.[1, 5, 6]

In the treatment of primary hypercholesterolemia, the combination can be used as an adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), LDL cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-HDL-C. Use of simvastatin/ezetimibe can also increase HDL cholesterol (HDL-C) in patients with primary (heterozygous familial and non familial) hypercholesterolemia or mixed hyperlipidemia.

Simvastatin/ezetimibe for homozygous familial hypercholesterolemia can be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Therapy with lipid-lowering agents such as simvastatin/ezetimibe should be one component of a multiple risk factor intervention program for individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Additionally, secondary causes for dyslipidemia (e.g. diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C (e.g. progestins, anabolic steroids, and corticosteroids), should be excluded and/or treated.

Simvastatin/ezetimibe is contraindicated in patients with hypersensitivity to either component of the medication, active liver disease or persistent elevations in serum transaminases, and during pregnancy and lactation.

IV. Pharmacokinetics

Absorption
The simvastatin/ezetimibe combination is bioequivalent to coadministered simvastatin and ezetimibe.[1]

Simvastatin
Absorption of simvastatin in animal dosing studies, has been estimated at 85% of the oral dose.[1] Plasma levels of simvastatin were not affected when the drug was administered immediately before an American Heart Association recommended low-fat meal.

Ezetimibe
Ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe glucuronide).[1, 6] After a single 10mg dose of ezetimibe, mean peak plasma concentrations of 3.4 to 5.5ng/ml were attained within 4 to 12 hours. There is no substantial deviation from dose proportionality between 5 and 20mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on intersubject variability, was 35% to 60% for area under the curve (AUC) values. Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered at 10mg tablets. However, the Cmax value of ezetimibe was increased by 38% with consumption of high fat meals.

Distribution
Simvastatin and its metabolite are highly bound (approximately 95%) to human plasma proteins. Both ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.[1]

Metabolism/Excretion
Simvastatin
Simvastatin is hydrolyzed in vivo to beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase.[1, 6] The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid of simvastatin and its 6'-hydroxymethyl, and 6'exomethylene derivatives. Peak concentrations of the drug occur at 4 hours and decline rapidly to about 10% of peak by 12 hours postdose. Simvastatin undergoes extensive first-pass extraction in the liver, with subsequent excretion of drug equivalents in the bile. As a result of this extraction of simvastatin (>60%), the availability of simvastatin to the general circulation is low. Following oral doses, 13% of the dose is excreted in urine and 60% in feces. One study suggested less than 5% of an oral dose of simvastatin actually reaches the general circulation as an active inhibitor.

Ezetimibe
Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion.[1, 6] Ezetimibe and ezetimibe-glucuronide are the main drug-derived components detected in the plasma, constituting 10%-20% and 80%-90% of the total drug in plasma, respectively. Both drug components are slowly eliminated from plasma, with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Data suggest some enterohepatic recycling of these components during metabolism. Ezetimibe is recovered in the feces and urine (78% and 11%, respectively), and ezetimibe is the major component in feces and accounts for 69% of the administered dose. The major component in urine is ezetimibe-glucuronide.

Table 2. Pharmacokinetic Parameters of Simvastatin/Ezetimibe[1, 5, 6]

Drug	Bioavailability	Protein Binding	Metabolism	Active Metabolites	Elimination	Half-Life
Simvastatin	85%	95%	Liver-hydroxylation	Yes	Feces (60%) and renal (13%)	-
Ezetimibe	35%-60%	>90%	Liver and small intestine	Yes	Biliary and renal	22 hours

V. Drug Interactions

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin.[1] Specific pharmacokinetic drug interaction studies with Vytorin® have not been performed. Table 3 lists the Level 1 and 2 drug-drug interactions documented with simvastatin and ezetimibe. Other non-classified interactions are described below the table.

Table 3. Clinically Significant Drug Interactions with Simvastatin and Ezetimibe[7]

Significance	Interaction	Mechanism
Level 1 Delayed, major, suspected	Simvastatin and Protease Inhibitors	Inhibition of simvastatin first-pass metabolism (CYP3A4) in the GI tract is suspected, resulting in elevated simvastatin plasma levels and increased risk of side-effects (e.g. rhabdomyolysis).
Level 1 Delayed, major, probable	HMG-CoA Reductase Inhibitors (including simvastatin) and Macrolide Antibiotics	Inhibition of metabolism (CYP3A4) is suspected and may lead to severe myopathy or rhabdomyolysis from elevated HMG-CoA reductase inhibitor levels.
Level 1 Delayed, major, probable	HMG-CoA Reductase inhibitors (including simvastatin) and Cyclosporine	Decreased metabolism of HMG-CoA reductase inhibitors is suspected and may cause increased levels and side-effects of HMG-CoA reductase inhibitors.
Level 1 Delayed, major, suspected	HMG-CoA Reductase Inhibitors (including simvastatin) and Gemfibrozil	Mechanism is unknown. Severe myopathy or rhabdomyolysis may occur.
Level 1 Delayed, major, suspected	HMG-CoA Reductase Inhibitors (including simvastatin) and Nefazodone	Possible nefazodone inhibition of metabolism of HMG-CoA reductase inhibitors metabolized by the CYP3A4 isozyme. The risk of HMG-CoA reductase inhibitor-induced rhabdomyolysis and myositis may be increased with HMG-CoA reductase inhibitors.
Level 2 Delayed, moderate, probable	HMG-CoA Reductase inhibitors (including simvastatin) and Verapamil	Possible inhibition of first-pass metabolism (CYP3A4) of the HMG-CoA reductase inhibitors, leading to elevated plasma concentrations of the HMG-CoA reductase inhibitors and increase risk of toxicity.
Level 2 Delayed, moderate, probable	HMG-CoA Reductase inhibitors (including simvastatin) and Diltiazem	Possible inhibition of first-pass metabolism (CYP3A4) of the HMG-CoA reductase inhibitors, leading to elevated plasma concentrations of the HMG-CoA reductase inhibitors and increase risk of toxicity.
Level 2 Delayed, moderate, suspected	HMG-CoA Reductase inhibitors (including simvastatin) and Bile Acid Sequestrants	The HMG-CoA reductase inhibitor may absorb to the bile acid sequestrant, reducing the GI absorption of the HMG-CoA reductase inhibitor, causing a reduction in the HMG-CoA reductase inhibitor effect.
Level 2 Delayed, moderate, suspected	Warfarin and HMG-CoA Reductase Inhibitors (including simvastatin)	Inhibition of warfarin hepatic metabolism is suspected causing the anticoagulant effect of warfarin to be increased.
Level 2 Rapid, moderate, probable	HMG-CoA Reductase Inhibitors (including simvastatin) and Azole Antifungals	Azole antifungals may inhibit the first-pass hepatic metabolism of HMG-CoA reductase inhibitors, leading to increased plasma levels and side effects of the HMG-CoA reductase inhibitors.
Level 2 Moderate, suspected	HMG-CoA Reductase Inhibitors (including simvastatin) and Grapefruit Juice	Inhibition of first-pass metabolism (CYP3A4) of HMG-CoA reductase inhibitors in the small intestine, leading to increased serum levels and side-effects of the HMG-CoA reductase inhibitors.
Level 2 Delayed, moderate, suspected	HMG-CoA Reductase Inhibitors (including simvastatin) and the Rifamycins	Rifamycins may induce first-pass metabolism (CYP3A4) of the HMG-CoA reductase inhibitors in the intestine and liver or may affect other intestinal transport mechanisms. The effect is a reduction in HMG-CoA reductase inhibitor levels, decreasing the pharmacologic effects of those drugs.

Simvastatin
Simvastatin is a substrate for CYP3A4. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (as indicated by some the interactions described in Table 3). Simvastatin is not an inhibitor of CYP3A4, and, therefore, is nor expected to affect the plasma levels of other drugs metabolized by CYP3A4.[1]

Ezetimibe
In a study of 12 individuals, ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4).[1] This indicates ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isoenzymes, and is unlikely to affect the metabolism of drugs that are metabolized by these enzymes.

- Antacids: Administration of an aluminum and magnesium containing antacid decreased the Cmax of ezetimibe 30%, but had no significant effect on the AUC.
- Cholestyramine: Coadministration decreased the mean AUC of ezetimibe approximately 55%. The incremental LDL-C reduction caused by adding ezetimibe to cholestyramine may be reduced.
- Fibric acid derivatives (fenofibrate and gemfibrozil): Coadministration of ezetimibe with fenofibrate or gemfibrozil increased the total ezetimibe concentration 1.5 and 1.7-fold, respectively. Because fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis, and ezetimibe was shown in animal studies to increase cholesterol in the gallbladder bile, concomitant use is not recommended until use in patients is studied.
- Cyclosporine: Total ezetimibe level increased 12-fold in 1 transplant patient receiving multiple medications, including cyclosporine. Close monitoring is essential.

VI. Adverse Drug Events

Warnings and Precautions
Myopathy and Rhabdomyolysis: In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with placebo or HMG-CoA reductase inhibitor alone.[1] Myopathy and rhabdomyolysis are known to be adverse events with the HMG-CoA reductase inhibitors and other lipid-lowering agents. The incidence of CK (creatine kinase) >10 times the upper limit of normal, in studies with Vytorin®, was 0.2%.

The risk of myopathy is increased by higher plasma levels of HMG-CoA reductase inhibitors, and is dose related for simvastatin. The risk of myopathy/rhabdomyolysis is increased with the following: potent inhibitors of CYP3A4, gemfibrozil, other fibrates including = 1g/day of niacin, and amiodarone or verapamil. In clinical trials, the incidence of myopathy/rhabdomyolysis has been 0.02% at 20mg, 0.07% at 40mg, and 0.3% at 80mg.

The incidence of consecutive elevated liver enzymes (= 3 times ULN) in serum transaminases was 1.7% overall for patients treated with simvastatin/ezetimibe.[1] Elevations appeared to be dose related with an incidence of 2.6% for patients treated with simvastatin/ezetimibe10/80mg. In controlled long-term (48 week) extensions, the incidence of consecutive elevations (= 3 times ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with simvastatin/ezetimibe 10/80mg. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before initiation of simvastatin/ezetimibe, and after therapy has been started, when clinically indicated, and more frequently in patients titrated to the 10/80mg dose (three months after titration to the 10/80mg dose, and periodically thereafter for the first year of treatment).

Simvastatin/ezetimibe has been evaluated in more than 3,800 patients in clinical trials. Table 4 lists the common adverse events with simvastatin/ezetimibe.

Table 4. Adverse Events in =2% of Patients Treated with Simvastatin/Ezetimibe (n=1,236)*[1]

Body System/Organ Class	Placebo (%) n=311	Ezetimibe 10mg (%) n=302	Simvastatin** (%) n=1,234	Vytorin®** (%) n=1,236
Body as a Whole-general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and Infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and Connective Tissue Disorders				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

*Data included from three similarly designed, placebo-controlled trials. Events occurring at an incidence greater than placebo, regardless of causality. Data includes two placebo-controlled studies in which the active ingredients equivalent to Vytorin® were coadministered and one placebo-controlled study in which Vytorin® was administered.

Other adverse events reported for **simvastatin** in placebo-controlled trials, regardless of causality assessment: asthenia, cataract, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, eczema, pruritus, and rash.[1]

Other adverse events reported for **ezetimibe** in placebo-controlled trials, regardless of causality assessment: fatigue, abdominal pain, diarrhea, viral infection, pharyngitis, sinusitis, arthralgia, back pain, and coughing.[1] The following adverse events have been reported in post-marketing experiences: hypersensitivity reactions including angioedema and rash, pancreatitis, nausea, cholelithiasis and cholecystitis.

VII. Dosing and Administration

Simvastatin (Zocor®) and ezetimibe (Zetia®), when given as single entity agents, are administered as once daily medications.

Table 5. Dosing and Administration with Simvastatin/Ezetimibe (Vytorin®)[1, 5, 6]

Drug	Dosing
Simvastatin/Ezetimibe (Vytorin®) Available in capsule shaped tablets: 10/10, 10/20, 10/40, and 10/80 (mg ezetimibe/ mg simvastatin)	Simvastatin/ezetimibe should be taken as a single daily dose, in the evening, with or without food. The dose should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. Starting dose: 10/20mg/day (10/10mg for less aggressive LDL-C reductions, and 10/40mg for larger reductions in LDL-C (>55%)) Dose range: 10/10mg/day through 10/80mg/day Titration: After initiation of therapy, lipid levels may be analyzed after two or more weeks and the dose adjusted, if necessary. Homozygous Familial Hypercholesterolemia: 10/40mg/day or 10/80mg/day in the evening. Note: The dose of simvastatin/ezetimibe should not exceed 10/10mg daily in patients concomitantly taking cyclosporine. Dosing of simvastatin/ezetimibe should occur either =2 hours before or =4 hours after administration of a bile acid sequestrant. Patients taking amiodarone or verapamil with simvastatin/ezetimibe should not exceed 10/20mg/day.

Special Dosing Considerations

Table 6. Special Dosing Considerations with Simvastatin/Ezetimibe[1, 5, 6]

Drug	Renal Dosing	Hepatic Dosing	Pediatric Use	Pregnancy Category	Can Dosage Form Be Crushed
Simvastatin/ Ezetimibe	No dose adjustment for mild or moderate renal insufficiency; with severe renal insufficiency, simvastatin/ ezetimibe should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5mg of larger. Close monitoring is necessary.	No dose adjustment is needed for patients with mild hepatic insufficiency.	Insufficient data exist for the safe and effective use of simvastatin/ ezetimibe in pediatric patients.	X	Per the manufacturer, no data is available on the bioavailability or efficacy of crushing the simvastatin/ ezetimibe tablets.

VIII. Effectiveness

Table 7 describes the clinical efficacy studies for simvastatin/ezetimibe.

Vytorin® is considered equivalent to simvastatin coadministered with ezetimibe; therefore, many clinical trials conducted to evaluate the efficacy of Vytorin® were initiated with simvastatin and ezetimibe concomitantly during the study period.[1]

Table 7. Clinical Efficacy Studies for Simvastatin/Ezetimibe (Vytorin®)

Study Design	Sample	Treatment and Duration	Results
Multicenter, double-blind, placebo-controlled trial[1, 8]	n=1,528	12 week trial of ten different treatments: ezetimibe 10mg, simvastatin 10mg, 20mg, 40mg, 80mg,or Vytorin® 10/10, 10/20, 10/40, or 10/80	• When patients receiving Vytorin® were compared to those receiving all doses of simvastatin (monotherapy), Vytorin® significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. • Vytorin® also produced significantly greater reductions in LDL-C compared to simvastatin monotherapy at each individual dose comparison ($p<0.001$). • The LDL-C reduction observed with Vytorin® was significantly greater compared to each next highest dose of simvastatin ($p<0.001$). • Pooled Vytorin® therapy significantly reduced the following other lipid parameters compared to pooled simvastatin: non-HDL-C (-49% vs. –36%, $p<0.001$); apolipoprotein B (-42% vs. –32%, $p<0.001$); TG (-24 vs. –21%, $p<0.001$). • The effects of Vytorin® on HDL-C were similar to the effects with simvastatin but were significantly greater compared with placebo. • Overall safety was similar across all treatment groups. • There were no reports of rhabdomyolysis in the treatment groups and the incidence of creatine kinase elevations =10 ULN was comparable between the treatment groups. • The incidence of transaminase elevations = 3 X ULN was comparable among patients receiving Vytorin® and

			simvastatin. • Table 8 describes the percent change in lipid parameters from baseline after 12 weeks of treatment.
Multicenter, double-blind, controlled trial [1, 9]	n=710	23 week study of four treatment groups: Vytorin® 10/10, 10/20, and 10/40, or simvastatin 20mg	In patients with known CHD or CHD risk equivalents and LDL-C = 130mg/dL and triglycerides = 350mg/dL were randomized to one of the four treatment regimens: • After five weeks of treatment, all doses of Vytorin® provided significantly greater LDL-C reductions compared with simvastatin 20mg monotherapy. A greater number of patients on Vytorin® 10/10, 10/20, and 10/40 achieved target LDL-C goal of <100mg/dL compared to simvastatin 20mg monotherapy. • 83% of the patients on Vytorin® achieved goal LDL-C <100mg/dL on the starting dose of Vytorin® (10/20) versus 46% who reached goal on simvastatin 20mg monotherapy. • Table 9 describes the percent reduction in LDL-C and goal attainments after five weeks of treatment. • Vytorin® was well tolerated and the incidence of clinical adverse events was similar between the groups. • Two patients in the simvastatin monotherapy group and one patient receiving Vytorin® had CK = 10 X ULN and two patients who received Vytorin® had consecutive elevations in transaminases = 3 X ULN.
Multicenter, double-blind, forced titration study[1, 10]	n=788	Four 6-week study periods of one of three treatment groups: Atorvastatin 10, 20, 40, or 80mg or Vytorin® 10/10, 10/20, 10/40 or 10/80 (Group 3 started at 10/20 instead of 10/10)	After four weeks of diet/placebo, patients who had not attained NCEP ATP III target LDL-C goal, were randomized to one of three treatment groups for four 6-week periods: • At the end of Period 1, the mean LDL cholesterol reduction was significantly greater with Vytorin® 10/10mg/day (46%) and Vytorin® 10/20mg/day (50%) than with atorvastatin 10mg/day (37%; both p = 0.05%), and the mean HDL cholesterol increase was greater (8.0% and 10% vs. 5%; both p= 0.05). • At the end of Week 4, when max doses of the drugs were administered, Vytorin® 10/80mg/day caused a greater mean LDL cholesterol reduction than did atorvastatin 80mg/day (59% vs. 53%) and a greater mean increase in HDL cholesterol (12% vs. 6%; both p= 0.005). • Vytorin® was superior to atorvastatin in decreasing LDL-C at each dose. Table 10 further describes the lipid parameters from baseline for all treatment periods. • The safety of Vytorin® was observed to be similar to that of atorvastatin monotherapy.
12-week multicenter, randomized, double-blind study[11]	n=887	12-week study of co-administered ezetimibe and simvastatin equivalent to Vytorin®, with simvastatin monotherapy	Patients with primary hypercholesterolemia were given ezetimibe and simvastatin (10/10, 10/20, 10/40, or 10/80), simvastatin monotherapy, or placebo: • Coadministration of ezetimibe/simvastatin (pooled data) led to a mean percent reduction in LDL-C levels from baseline to study end point of –53% compared with a reduction of –38% with simvastatin alone (pooled). • The incremental mean percent LDL-C reduction for pooled ezetimibe/simvastatin vs. pooled simvastatin alone was 14.8% (p<0.001). • The percent reduction in LDL-C with ezetimibe/simvastatin at any given simvastatin dose was significantly greater than that seen with the next higher dose of simvastatin alone

			(p<0.001 for all between-group comparisons). • The mean percent reduction from baseline in LDL-C levels at study end point obtained with ezetimibe/simvastatin at 10/10mg was numerically similar to that with simvastatin 80mg alone. • A greater number of patients in the ezetimibe plus simvastatin treatment group reached LDL-C goal of <100mg/dL compared to simvastatin monotherapy (82% vs. 43%, p<0.001). • Coadministration of ezetimibe and simvastatin also resulted in significant improvements in TC, non-HDL-C, TG, Apo B, LDL-C:HDL-C, and TC:HDL-C (p<0.001 for between group comparisons).
Multicenter, double-blind, placebo-controlled study[1, 12]	n=668	12-week study of ezetimibe coadministered with simvastatin (equivalent to Vytorin® 10/10, 10/20, 10/40, 10/80) with simvastatin monotherapy	In patients with primary hypercholesterolemia: • Ezetimibe coadministered with simvastatin was significantly more effective than simvastatin monotherapy in reducing plasma LDL-C levels from baseline to end point (-49.9% vs. 36.1%). • The combination resulted in a significant 13.8% LDL-C reduction compared with pooled simvastatin alone (p<0.01). • Mean percentage changes in direct LDL-C from baseline to end point ranged from approximately –44% to –57% for coadministration versus –27% to –44% for simvastatin monotherapy. • NCEP ATP III goal was reached by 77% of patients receiving coadministration therapy (pooled data) versus 64% who received simvastatin monotherapy (p<0.01). • Tolerability of the combination was similar to that of simvastatin and placebo. • Eight patients, six receiving coadministration therapy and two receiving simvastatin monotherapy, had consecutive elevations = 3X ULN for ALT and/or AST levels. However, activity was asymptomatic and no cases of hepatitis, jaundice, or signs of liver dysfunction were reported.
Multicenter, randomized, double-blind, parallel group study[1, 13]	n=214	Following six weeks of simvastatin 20mg/day, patients received the addition of either ezetimibe 10mg/day or simvastatin 20mg/day, for 24 weeks.	In diabetic patients stable on a thiazolidinedione, with hypercholesterolemia: • Coadministered ezetimibe plus simvastatin was significantly more effective than doubling the dose of simvastatin to 40mg. • Median changes from baseline for the combination were: LDL-C:25% and –5%; total-C:16% and –5%; Apo B: -19% and –5%, and non-HDL-C: -23% and –5%. Results for the HDL-C and TG between the two treatment groups were not significantly different. • 33% of patients were above goal for LDL-C at randomization. Of these, 75.7% in the ezetimibe + simvastatin 20mg group versus 39.4% in the simvastatin 40mg only group had LDL-C <100mg/dL at the end of the study. • 2.7% of the simvastatin monotherapy patients and 1.0% of the ezetimibe + simvastatin patients discontinued therapy due to treatment-related adverse events. • There were no cases of myopathy.

Randomized, double-blind study of co-administration of ezetimibe plus a statin (atorvastatin or simvastatin)[1, 14]	n=50	12-week study of atorvastatin or simvastatin 80mg, ezetimibe 10mg plus atorvastatin or simvastatin 40mg, or ezetimibe 10mg plus atorvastatin or simvastatin 80mg	In patients with homozygous familial hypercholesterolemia already receiving statin treatment plus NCEP or stricter diet: • Ezetimibe plus statin significantly reduced LDL-C levels compared with the 80mg statin dose alone (-20.7% vs. –6.7%, p=0.007). • In high-dose statin cohorts, ezetimibe plus statin 80mg reduced LDL-C by an additional 20.5% (p=0.0001). • Increasing the dose of simvastatin from 40mg to 80mg produced a reduction of LDL-C of 13% from baseline on simvastatin 40mg. • Coadministration of ezetimibe and simvastatin (equivalent to Vytorin® 10/40 and 10/80 pooled), produced a reduction of LDL-C of 23% from baseline on simvastatin 40mg. • In patients previously on baseline simvastatin 40mg, coadministered ezetimibe and simvastatin (10/80), produced a reduction in LDL-C of 29%. • One patient in the statin 80mg group and one patient in the ezetimibe plus statin group had asymptomatic single transient increases in serum ALT and/or AST >3 X ULN. • There were no episodes of myopathy or rhabdomyolysis.

Table 8. Mean Percent in Lipid Parameters from Baseline After 12 Weeks of Treatment[1]

Treatment	LDL-C	HDL-C	TG (Median)	Non-HDL-C	Total C	Apo B
Vytorin® (n=609) (pooled data)	-53**	+7	-24**	-49**	-38**	-42**
Simvastatin (n=622) (pooled data)	-39	+7	-21	-36	-28	-32
Ezetimibe 10mg (n=149)	-19	+5	-11	-18	-13	-15
Placebo (n-148)	-2	0	-2	-2	-1	0
Vytorin® 10/10 (n=152)	-45*	+8	-23	-41*	-31*	-35*
Simvastatin 10mg (n=158)	-33	+5	-17	-30	-23	-26
Vytorin® 10/20 (n=156)	-52*	+10	-24***	-47*	-36*	-41*
Simvastatin 20mg (n=150)	-34	+7	-18	-32	-24	-28
Vytorin® 10/40 (n=147)	-55*	+6	-23	-51*	-39*	-44*
Simvastatin 40mg (n=156)	-41	+8	-21	-38	-29	-33
Vytorin® 10/80 (n=154)	-60*	+6	-31	-56*	-43*	-49*
Simvastatin 80mg (n=158)	-49	+7	-27	-45	-35	-39

*p<0.001 for Vytorin® compared with the corresponding dose of simvastatin.
**p<0.001 for pooled Vytorin® compared to pooled simvastatin.
***p=0.054 for Vytorin® compared with the corresponding dose of simvastatin.

Table 9. Percent Reduction in LDL-C and Goal Attainments After Five Weeks of Treatment[1, 9]

Treatment Group	Mean Baseline LDL-C Levels (mg/dL)	Percent Reduction in LDL-C Levels	Percent of Patients Attaining LDL-C <100mg/dL
Simvastatin 20mg (n=253)	174	-38%	46%
Vytorin® 10/10 (n=251)	165	-47%	75%
Vytorin® 10/20 (n=109)	167	-53%	83%
Vytorin® 10/40 (n=97)	171	-59%	88%

Note: P<0.001 for all doses of Vytorin® compared to simvastatin 20mg.

Table 10. Percent Change in Lipid Parameters from Baseline for All Treatment Periods [10]

	Treatment (n)	LDL-C	HDL-C	TG	Total C	Non-HDL-C	Apo B
Period 1 (Week 6)	Atorvastatin 10mg (n=262)	-37	+5	-23	-28	-35	-32
	Vytorin® 10/10 (n=263)	-46*	+8*	-26	-34*	-43*	-38*
	Vytorin® 10/20 (n=263)	-50*	+10*	-25	-36*	-46*	-41*
Period 2 (Week 12)	Atorvastatin 20mg (n=246)	-44	+7	-28	-33	-42	-38
	Vytorin® 10/20 (n=250)	-50*	+9	-28	-37*	-46*	-41*
	Vytorin® 10/40 (n=252)	-54*	+12*	-31	-39*	-50*	-45*
Period 3 (Week 18)	Atorvastatin 40mg (n=237)	-49	+8	-31	-37	-47	-42
	Vytorin® 10/40 (n=228)	-56*	+11*	-32	-40*	-52*	-45*
Period 4 (Week 24)	Atorvastatin 80mg (n=228)	-53	+6	-35	-40	-50	-45
	Vytorin® 10/80 (n=459)	-59*	+12*	-35	-43*	-55*	-49*

Note: p= 0.05 when comparing Vytorin® to atorvastatin within the specified week.

Additional Evidence

Dose Simplification: No clinical data is available for the combination of simvastatin/ezetimibe (Vytorin®), comparing adherence rates in patients given the combination agent versus therapy with each agent alone. Studies shown improved efficacy with simvastatin and ezetimibe therapy when administered concomitantly, but no studies have compared the combination agent with use of coadministration of simvastatin and ezetimibe.

Additionally, simvastatin and ezetimibe are both once-daily treatments, so the combination only offers patients the opportunity to take one less tablet per day, as compared to coadministration of each individual agent. No studies have evaluated or compared adherence with Vytorin® versus coadministration of simvastatin and ezetimibe.

Stable Therapy: A literature search of Medline and Ovid did not reveal clinical data on changing from other therapies to simvastatin/ezetimibe.

Impact on Physician Visits: A literature search of Medline and Ovid did not reveal clinical data pertinent to use of simvastatin/ezetimibe and impact on physician visits.

IX. Conclusions

Studies show positive benefits with statin therapy plus ezetimibe (Zetia®), as compared with statin monotherapy. Since the combination simvastatin/ezetimibe (Vytorin®) is considered equivalent to simvastatin coadministered with ezetimibe, and no studies have directly compared the efficacy of the different dosing regimens (combination therapy vs. coadministration of the agents), both regimens offer similar cholesterol lowering outcomes. Studies confirm the efficacy and safety of simvstatin/ezetimibe to be similar to the individual agents when administered separately. The combination product demonstrates no clinical advantage over simvastatin (Zocor®) and ezetimibe (Zetia®) when coadministered, with respect to cholesterol lowering outcomes.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand of simvastatin/ezetimibe (Vytorin®) is recommended for preferred status.

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